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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No.

USV PHARMACEUTICAL CORPORATION, PETITIONER

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

USV Pharmaceutical Corporation petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Fourth Circuit in this case.

OPINIONS BELOW

The opinion of the Court of Appeals (App. A, *infra,* pp. 1a-10a) is reported at 461 F.2d 223. The opinion of the United States District Court for the Eastern District of Virginia (App. D, *infra,* pp. 13a-16a, see also App. E and F, *infra,* pp. 17a-19a), not officially reported, has been reprinted at CCH Food Drug Cosm. L. Rep. ¶ 40,489.

JURISDICTION

The judgment of the Court of Appeals was entered on May 24, 1972 (App. B, *infra,* p. 11a). A petition for rehearing filed by USV was denied on July 5, 1972 (App. C, *infra,* p. 12a). The Chief Justice extended the time within which to file a petition for certiorari until October 30, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

QUESTIONS PRESENTED

The 1962 amendments to the Federal Food, Drug and Cosmetic Act of 1938 expanded the statutory definition of "new drugs", for which a new drug application must be approved by the Food and Drug Administration in advance of marketing, to include drugs "not generally recognized as *** effective ***" in addition to those "not generally recognized *** as safe ***". A "grandfather" provision, however, exempted drugs already on the market which were not "new drugs" as defined by the Act prior to amendment, and "not covered by an effective [new drug] application ***".

The questions are:

1. Whether the "grandfather" provision applies to pre-1962 drugs which had been the subject of a new drug application ("NDA") when first introduced, but which by the time of the amendments were concededly no longer "new drugs", and were no longer treated either by the manufacturer or by FDA as subject to the regulatory scheme applicable to NDA'd products.

2. Whether the "grandfather" provision is inapplicable to pre-1962 drugs which were never "new drugs" from the moment of their introduction and were never the subject of a new drug application, therefore literally qualifying for "grandfather" protection, merely

because they include the same principal ingredient as earlier products of the same manufacturer for which NDA's had originally been filed.

STATUTES INVOLVED

Pertinent provisions of the Federal Food, Drug and Cosmetic Act of 1938, § 201(p), 52 Stat. 1041, and of the Act as amended in 1962, Publ. L. No. 87-781, 76 Stat. 780, § 102(a)(1), 21 U.S.C. § 321(p)(1), and § 107(c)(4), 21 U.S.C.A. note following § 321, are set out in Appendix I, *supra,* pp. 50a-53a.

STATEMENT

1. During 1955 and 1956 the Commissioner of Food and Drugs approved three new drug applications ("NDA's") covering seven drug products of petitioner USV Pharmaceutical Corp. containing citrus flavonoid compound (App. A, *infra,* p. 2a). The recommended use of the products, as found by the District Court (App. D, *infra,* p. 16a), was control of abnormal capillary permeability and fragility.[1]

Under the statutory scheme then in effect, such prior Food and Drug Administration approval was required before marketing a "new drug", that is, a drug "not generally recognized by experts *** as safe" for its intended uses.[2] In the NDA, the manufacturer was re-

[1] This is a condition of the capillary walls which may result in easy surface bleeding such as in bruises (Transcript of Trial, pp. 288-89). The use of USV's bioflavonoid products for this purpose is recommended to physicians only. While no prescription is required to purchase these products, they are described merely as "a supplementary source of bioflavonoids" in the labeling made available to the lay purchaser (J.A. 187) ("J.A." refers to the Joint Appendix in the Court of Appeals).

[2] Federal Food, Drug, and Cosmetic Act of 1938, § 201(p)(1), 52 Stat. 1041.

quired to show that his product was in fact safe, and approval by FDA of the application constituted the agency's ratification of such proof.[3]

In 1957, USV developed two new bioflavonoid products ("Bivam" and "Duo-CVP with Vitamin K") similar in composition and labeling to the seven products for which new drug applications had been approved the previous year.[4] First obtaining specific advance advice from FDA that Bivam[5] was "generally recognized as safe" (GRAS), and hence not a "new drug", USV placed these "me-too" products on the market without filing NDA's.[6] At no time thereafter did FDA ever assert that either required an NDA.[7]

On February 28, 1961, satisfied that its bioflavonoid products previously covered by NDA's also were by then generally recognized as safe, USV sought an express FDA ruling that these products were no longer "new drugs".[8] In response, FDA advised the company on April 19, 1961 that two of the previously-NDA'd products "are not new drugs". As to the remainder, FDA said it had incomplete current marketing information to make a determination, but would

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[3] § 505(d), 52 Stat. 1052.

[4] App. D, *infra*, p. 15a. No additional labeling directed to physicians, recommending the product for abnormal capillary permeability and fragility, was disseminated for Bivam.

[5] No separate ruling was sought on Duo-CVP with Vitamin K.

[6] App. A, *infra*, p. 8a. In FDA regulatory parlance, a "me-too" product is one substantially identical to a previously-marketed product for which a new drug application has been approved but which subsequently became "generally recognized * * * as safe" (and, since 1962, effective), with the result that the copy is not a "new drug" and can therefore be marketed without an approved NDA. See App. A, *infra*, p. 7a.

[7] See J.A. 150.

[8] J.A. 33-34.

be "pleased" to rule upon receipt of the additional data.[9]

USV supplied such information within a month, noting its "recollection" that "a short time after the NDA became effective" (*i.e.*, in 1956-1957), the products "were no longer considered to be new drugs", and requesting FDA's "confirmation of the above".[10] FDA never responded.

It has traditionally been considered the responsibility of the manufacturer to decide, subject to severe penalties if he is later held to have decided incorrectly, whether his product is a "new drug" requiring premarketing approval by FDA.[11] Because the identical citrus flavonoid compound is contained in all USV bioflavonoid products, three of which FDA had expressly ruled were not "new drugs", USV concluded that the "not-new" status of all these products had been established, and thereafter discontinued filing with FDA the continuing reports and supplemental information required for NDA'd products.[12] Although FDA was thus fully aware of USV's position that the products were no longer "new drugs" within the meaning of the statute and that the company was treating each of them as no longer subject to the regulatory scheme applicable to NDA'd products, at no time was this challenged by the agency.

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[9] J.A. 35-36, 148.

[10] J.A. 37.

[11] *Bentex Pharmaceuticals, Inc.* v. *Richardson*, 463 F.2d 363 (4th Cir. 1972), App. G, *infra*, p. 22a, *petition for certiorari filed*, No. 72-555, October 5, 1972. See also Peter Barton Hutt, *Proper Classification of Products Under the Federal Food, Drug, and Cosmetic Act*, p. 3 (unpublished paper presented at Annual Convention of the Federal Bar Ass'n, Miami, Fla., Sept. 4, 1969).

[12] App. D, *infra*, p. 15a. The requirements then applicable were published at 25 Fed. Reg. 12595 (1960).

2. In 1962, the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act were enacted, expanding the definition of "new drug" to cover drugs not generally recognized by experts as "safe *and effective*" for their intended uses.[13] However, as to certain products generally recognized as safe prior to 1962, a "grandfather clause" contained in Section 107(c)(4) of the amending statute granted full exemption from the added efficacy element in the definition of "new drug", and preserved their right to remain on the market without advance FDA approval. To qualify for the § 107(c)(4) exemption, it must be shown that the product "on the day immediately preceding the enactment date" (*i.e.*, October 9, 1962) satisfied three conditions: (A) that it was commercially used or sold in the United States, (B) that it was not a new drug as defined in the Act as then in force (*i.e.*, was "generally recognized *** as safe"), and (C) that it was not "covered by an effective [new drug] application" under the Act.

Exemption from the expanded FDA preclearance requirement does not mean, of course, that the public is unprotected against false claims of efficacy for the drug in question. Untrue efficacy claims constitute "misbranding" in violation of the Act,[14] and subject the manufacturer to severe criminal and civil sanctions as well as seizure of the product and its removal from the market.[15]

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[13] Drug Amendments of 1962, § 102(a)(1), (2), *amending* Federal Food, Drug, and Cosmetic Act of 1938, § 201(p), 21 U.S.C. § 321(p).

[14] § 502, 21 U.S.C. § 352.

[15] *Bentex Pharmaceuticals, Inc.* v. *Richardson*, note 11 *supra*, App. G, *infra*, pp. 25a-26a.

The 1962 amendments also expanded the grounds upon which approval of an NDA could be denied or withdrawn by FDA. Prior to 1962, approval could be denied, and once granted could subsequently be revoked, only for insufficient evidence of safety. The 1962 amendments required FDA, in deciding whether to approve or revoke approval of new drug applications, to consider the evidence of efficacy as well. At any time after the expiration of a two-year "grace period",[16] moreover, FDA could initiate revocation proceedings as to pre-1962 NDA's which were still operative and, after "due notice and an opportunity for hearing to the applicant", withdraw approval previously granted upon a finding "that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have * * *".[17]

In July 1968, relying upon an adverse report on the efficacy of one of USV's bioflavonoid products rendered by the National Academy of Sciences/National Research Council Drug Efficacy Study which FDA had commissioned following the 1962 amendments, FDA initiated proceedings to revoke approval of the three bioflavonoid NDA's held by USV.[18] In light of FDA's prior position with regard to the products, however, the company believed that each of its bioflavonoid formulations satisfied the criteria for "grandfather" status under the 1962 amendments to the definition of "new drug", and that under the pre-1962 definition the products were not "new drugs". USV therefore

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[16] Drug Amendments of 1962, § 107(c)(3), 76 Stat. 788-89, 21 U.S.C.A. note following § 321.

[17] Drug Amendments of 1962, § 102(d), 76 Stat. 782, *amending* Federal Food, Drug, and Cosmetic Act of 1938, § 505(e), 21 U.S.C. § 355(e).

[18] J.A. 28, 30-31.

instituted the present action in the District Court for a declaratory judgment against the Secretary of Health, Education and Welfare and the Commissioner of Food and Drugs, who are charged with the administration of the Food, Drug and Cosmetic Act, which would confirm USV's right to continue to market the products even without an approved new drug application. A stay of the administrative revocation proceeding for the pendency of the declaratory judgment action was sought from FDA.[19]

3. The District Court (App. D, *infra*, pp. 13a-16a) rejected FDA's challenge to its jurisdiction (p. 14a) and, proceeding to the merits, held that USV was correct as to *all* its bioflavonoid products—those for which NDA approval had been granted when originally introduced as well as those "me-too" products for which no NDA had ever been filed. The court found Clauses (A) and (B) of § 107(c)(4) to be satisfied (*id.*, pp. 14a, 15a-16a; App. F, *infra*, p. 18a). It further found that,

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[19] The stay was denied, but no further action was taken by FDA to prosecute the revocation proceeding. In July 1970, contemporaneously with the setting of a trial date in the declaratory-judgment action, FDA sought to revive the revocation proceeding by calling upon USV to establish its right to a hearing under "summary judgment" regulations which the agency had promulgated in the interim. USV again moved for a stay pending disposition of the declaratory-judgment action (J.A. 39-41). Eight days before trial in the district court was scheduled to begin, FDA denied the stay and entered a final order of revocation, refusing to allow USV to contest the matter further (J.A. 42). The revocation order has since been set aside by the Court of Appeals for the District of Columbia Circuit for denial of "administrative due process", resulting from FDA's use of procedures which were "fundamentally defective • • • unsound and unfair" (*USV Pharmaceutical Corp.* v. *Secretary of HEW*, No. 24900, decided August 14, 1972, App. H, *infra*, pp. 46a, 48a). The Government has informed USV that "after reviewing the decision of the court in this matter, we have concluded not to seek certiorari" (Letter dated Oct 17, 1972 from Peter Barton Hutt, Esq. to Joel E. Hoffman, Esq.).

as a result of the actions of USV and of FDA's administrative treatment of the matter between the time USV filed its new drug applications and the enactment of the 1962 amendments, in which neither the manufacturer nor the agency treated the products as subject to the regulatory scheme applicable to NDA'd products, the previously-approved NDA's had been effectively withdrawn by USV in a practical sense prior to October 1962; hence "none of the plaintiff's bioflavonoid products in question were covered by an effective NDA as of October 9, 1962" (*id.*, p. 15a). Clause (C) of § 107(c)(4) was thus satisfied and the pre-amendment definition of "new drug" continued to apply under which the products were not "new drugs" (*ibid.*). The remedy for any untrue claims of efficacy, the District Court concluded, thus continued to be in criminal, injunction and seizure actions for unlawful "misbranding", rather than in administrative denial or revocation of marketing authority by FDA.

On appeal, after summarily affirming the jurisdictional ruling below,[20] the Court of Appeals considered separately the NDA'd and non-NDA'd drugs. Although both groups were found to satisfy Clauses (A) and (B) of § 107(c)(4), the court rejected the District Court's finding that the NDA's "had been effectively and practically withdrawn and that accordingly the

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[20] App. A, *infra*, p. 2a. The Court of Appeals invoked by reference the rationale it had set out in the companion case of *Bentex Pharmaceuticals, Inc.* v. *Richardson*, note 11 *supra*, App. G, *infra*. The Government's pending challenge to that decision thus necessarily calls into question the jurisdiction of the lower courts to decide the merits of the present case. See especially p. 18 n. 15 of the Solicitor General's Petition for Certiorari in *Bentex* (No. 72-555), which seems implicitly to take issue with the jurisdictional ruling here. That ruling is apparently also in conflict with *Ciba Corp.* v. *Richardson*, 463 F.2d 225 (3d Cir. 1972), *petition for certiorari filed*, No. 72-528, Oct. 2, 1972.

drugs were not covered by an effective NDA" on October 9, 1962 (App. A, *infra,* p. 4a).

"The error in this reasoning", the court below stated, "is that it assumes that a manufacturer may effect a withdrawal of an effective NDA, either by a formal notice or by discontinuing compliance with the reporting requirements for NDA'd drugs. * * * [H]e has no such right after approval of the application by the Secretary. At that point, only the Secretary can withdraw the approval". (App. A, *infra,* pp. 4a-5a.) Thus, in the view of the Court of Appeals, the District Court erred in finding that there had been a practical and effective withdrawal of the new drug applications by USV; no such action was permitted under the law and, since the Secretary had undertaken no action to withdraw *approval* of the applications, the products were still covered (*id.,* p. 5a).

The Court of Appeals additionally rejected an alternative theory which it found implicit in USV's argument: that since all the products involved had concededly become "generally recognized * * * as safe" prior to October 9, 1962, they had ceased to be "new drugs" and therefore the "previously issued NDA's were no longer needed or 'effective' ". This theory, the court said, "would make surplusage of requirement (C) in the exemption statute" and by thus treating (C) as a "nullity" would offend "the well settled rule of statutory construction that all parts of a statute are to be given an effect if at all possible". (*Id.,* pp. 5a-6a.)

The court acknowledged that a separate problem existed as to USV's two non-NDA'd "me-too" products. Facially, they were exempt under the plain language of § 107(c)(4) since they were admittedly "generally recognized *** as safe" from the outset and had *never* been "covered" by an effective NDA (*id.,* p. 6a).

Moreover, most commentators, while admitting the "incongruity" of a result which would exempt "me-too" products but not their pioneer NDA'd products, considered the result "compelled by the literal language of the statute". FDA's contention to the contrary in the course of this litigation had already been "severely criticized and with considerable reason". The argument was "at variance with the uniform position [FDA] has taken over the years with regard to the nature of NDA's", which, simply stated, was that the NDA is "personal" to drugs "as individual articles, not as collective groups". (*Id.*, p. 8a.)

Yet, having thus accepted the argument for exempting "me-too" drugs generally, the Court of Appeals nevertheless ruled that USV's "me-too's" were not entitled to the exemption. The company's "me-too's" were "similar in formula and labeling" to its NDA'd drugs; these NDA's were "personal" to USV; thus, the court reasoned, they covered not only the specific NDA'd products but also "all others like in formula". And, since the NDA'd products were disqualified, the two non-NDA'd products must derivatively fall. The court conceded that "this conclusion places [USV] in a less favorable position than [other manufacturers] who may have copied its product prior to October 9, 1962", but the inequity created by its decision could only be redressed, it held, by Congress. (*Id.*, p. 10a.)

REASONS FOR GRANTING THE WRIT

The decision of the Court of Appeals in this case presents questions of large importance in the administration of the Food, Drug and Cosmetic Act, relating to the legal scope and practical application of the "grandfather" provision contained in the 1962 amend-

ments. Definitive and prompt resolution of these issues, which can come only from this Court, is required in the interest of orderly and manageable enforcement of the Act. Review by this Court would remove the existing confusion and uncertainty surrounding this problem, would obviate further litigation, and would be helpful both to FDA, which must administer the statute in accordance with Congress' intentions, and to manufacturers who must know what the statute means in order to comply with it.

1. *The Importance of the Issues.* In attempting explicitly to delineate the precise circumstances in which the various 1962 drug amendments would apply to products already on the market, Congress demonstrated its judgment that the new classification criteria, testing requirements, burdens of proof, and reporting obligations were inappropriate for blanket retroactive imposition. Yet ever since enactment of the 1962 amendments the complex language of § 107(c)(4)'s "grandfather" provision has made its application confused and uncertain.

In straining for a simple and superficially equitable approach, however, the decision below improperly ignores the balance struck by Congress, disregarding this Court's admonition that "in our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop" (*62 Cases of Jam* v. *United States,* 340 U.S. 593, 600 (1951)).[21] Nor has even-handed enforcement of the Act been simplified; the Court of Appeals' decision, if unreviewed, would leave § 107(c)(4) in even greater

[21] See also *United States* v. • • • *Decholin,* 264 F.Supp. 473, 480, 482-83 (E.D. Mich. 1967).

disarray for the future. The right to market a range of concededly safe pre-1962 drugs remains unresolved; the administrative processes of FDA are burdened, despite the agency's repeated protests that its statutory duties exceed its resources; and manufacturers such as USV, who prior to 1962 expended their energies and resources to develop and market new drugs under FDA's complex NDA procedures, are forever saddled with expensive and burdensome restrictions despite the fact that the drugs are now generally recognized as safe, while others are forever exempted who simply copied the products of such innovative firms.

The number of long-marketed drugs affected by the decision below, although difficult to estimate precisely, is undoubtedly large. New drug applications for approximately 7,100 products were approved by FDA between 1938 (when the Food, Drug and Cosmetic Act became law) and 1962.[22] FDA advised Congress in 1969 that about 1,000 of these were contended by their manufacturers to have become "generally recognized *** as safe", and thus no longer "new drugs", in the years between approval of the NDA and 1962.[23] It would be conservative to assume that in at least a substantial number of these instances the manufacturers accordingly ceased compliance (as did USV) with the reporting and approval requirements applicable to "new drugs". The number of "me-too" copies involved may be as high as 13,000, if the Government is correct that an average of some 13 copies for which no NDA was

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[22] See Solicitor General's Petition for Certiorari, p. 5, *Richardson* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555, filed Oct. 5, 1972.

[23] *Hearings on Drug Efficacy Before a Subcommittee of the House Committee on Government Operations*, 91st Cong., 1st Sess. 375 (1969).

ever approved are now being marketed for each drug NDA'd prior to 1962.[24]

The substantive issues decided below, no less than the threshold jurisdictional and procedural issues in the companion cases before the Court,[25] are thus "of great importance to the Food and Drug Administration and the drug industry * * *" (Solicitor General's Petition for Certiorari, p. 20, No. 72-394 (*Hynson*)). Unless these substantive issues are settled now, extensive further litigation in the lower courts will inevitably ensue. Plenary review by the Court at this time is plainly warranted.[26]

2. *The Error as to Previously-NDA'd Products.* The District Court found that USV's actions subsequent to approval of its original NDA's—affirmed or ac-

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[24] Solicitor General's Petition for Certiorari, pp. 16-17 n. 14, *Richardson* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555, filed Oct. 5, 1972.

[25] *Richardson* v. *Hynson, Westcott & Dunning, Inc.*, No. 72-394, *petition for certiorari filed*, Sept. 7, 1972; *Hynson, Westcott & Dunning, Inc.* v. *Richardson*, No. 72-414, *petition for certiorari filed*, Sept. 11, 1972; *Ciba Corp.* v. *Richardson*, No. 72-528, *petition for certiorari filed*, Oct. 2, 1972; *Richardson* v. *Bentex Pharmaceuticals, Inc.*, No. 72-55, *petition for certiorari filed*, Oct. 5, 1972.

[26] The manufacturer's cross-petition for certiorari in the *Hynson* case (No. 72-414) seeks to raise, *inter alia*, the issue here presented as to products which once were covered by a new drug application. Unlike the products involved in *Hynson*, however, USV's bioflavonoid products have been the subject of a full evidentiary trial on the questions (a) whether the factual prerequisites to exemption from the change in the definition of "new drug" are met, and (b) whether the products are in fact "new drugs" under the definition prior to amendment. Regardless of the Court's decision to grant or deny the petition in No. 72-414, therefore, we submit that the issues raised by the instant petition for certiorari are both ripe and properly presented.

quiesced-in by FDA—amounted in practical terms to withdrawal of the NDA's prior to October 9, 1962. Thus, *a priori,* they could not on that date have been "covered by an effective application" and § 107(c)(4)'s third criterion for "grandfather" exemption was met.

The Court of Appeals disagreed. There was no provision in the statute for an applicant's "withdrawal" of an NDA once approved; the only "withdrawal" contemplated was withdrawal of approval by FDA, under the authority of § 505(e), and here approval had not been withdrawn. Thus, the court concluded, the products remained "covered" by effective NDA's on the date of the new statute.

But the court's preoccupation with whether USV had the "right" to "withdraw" its NDA misconceives the critical inquiry. Regardless of how the District Court had formulated the issue, the question on appeal was not whether USV had withdrawn its NDA, or indeed even whether USV had a right to "withdraw". Properly stated, the only question was whether USV's bioflavonoid products which had earlier been NDA'd were, on October 9, 1962, still "covered by an effective [new drug] application".

The District Court relied upon the sequence of events between the time of the filing of these NDA's and the 1962 amendments for its finding of practical and effective withdrawal of the NDA's prior to October 9, 1962, and on this basis concluded that thereafter the products were no longer "covered". In its preoccupation with the abstract question whether USV lawfully could "withdraw" its NDA, the court below ignored the underlying facts found by the District Court, which showed that by 1962 the products involved

were no longer being treated by either the manufacturer of FDA as subject to the regulatory scheme applicable to NDA'd products. These facts, we submit, surely justified the District Court's ultimate conclusion thaton October 9, 1962, the products were no longer "covered" by an effective NDA.[27]

Nor is the Court of Appeals' contrary ruling supported by § 505(e), the sole authority discussed in the opinion. In essence, the court said, once a product is NDA'd, it is forever NDA'd—unless FDA itself withdraws approval of the NDA under § 505(e). But, as the court itself recognized in upholding the jurisdiction of the District Court to entertain this action, FDA is wholly without authority to consider or decide in approval-revocation proceedings under § 505(e) whether a product previously approved continues to be a "new drug",[28] and that issue cannot be raised by either party in a § 505(e) proceeding. That provision cannot be invoked to terminate NDA coverage on the ground that the product has become GRAS and therefore is no longer a "new drug" requiring the regulatory oversight imposed on NDA'd products. Section 505(e) is a pro-

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[27] The District Court found (App. D, *infra*, pp. 14a-15a):

"The plaintiff made that clear through its correspondence with the Federal [sic] Drug Administration. It then ceased compliance with the submittal of data and new labeling, as required by the Federal Drug Administration for products covered by effective NDA's—The record further discloses that the Federal Drug Administration advised the plaintiff in writing that its products covered by [two of the NDA's] were not new drugs—and it was stipulated that the compound in these two products is identical to the bioflavonoid compound in plaintiff's other products and that the recommended uses of all of the [bioflavonoid] products are essentially the same."

[28] The court's rationale was elaborated in the companion case of *Bentex Pharmaceuticals, Inc.* v. *Richardson*, note 11 *supra*, App. G, *infra*. The Solicitor General is petitioning for certiorari to review that ruling (No. 72-555), which is also challenged in *Hynson, Westcott & Dunning, Inc.* v. *Richardson*, No. 72-414, *supra*.

vision of limited scope, permitting FDA to withdraw approval of an NDA only for the very opposite reason —that the evidence no longer shows the product to be safe (or, under the new statute, effective) and hence no longer allows the product to be marketed.

Perhaps misled by its assumption that the abbreviation "NDA" stands for "New Drug *Approval*" rather than for "New Drug *Application*" (see *Bentex Pharmaceuticals, Inc.* v. *Richardson*, note 11 *supra*, App. G, *infra*, p. 21a n.2), the court below nevertheless confused "withdrawal" *of the NDA*, as found by the district court, with "withdrawal *of approval*", as provided for in § 505(e). But § 505(e) does not, as we have shown, prescribe the procedures for terminating coverage of an NDA because the drug involved has become generally recognized as safe (or, since 1962, effective) and need no longer be subject to NDA regulation. So the fact that FDA never revoked approval of the NDA's involved in this case by proceeding under § 505(e) is simply irrelevant.

If an approved NDA which has become superfluous may be retired on that ground (and common sense says it may and should), then the procedure for doing so must be inferred from the whole scheme and purpose of the statute. And it strains both reason and common sense to hold that though the GRAS status of a product has been asserted by the manufacturer, ratified by FDA, acted upon by the manufacturer (in discontinuing all NDA reports) and acquiesced-in by FDA (in no longer imposing NDA controls), the product is nevertheless still "covered by an effective [new drug] application" because there has been no resort to the formal revocation-of-approval procedures of § 505(e), which can be initiated only by FDA, extend only to the precisely opposite situation, and therefore could not have been invoked by USV to terminate the coverage of its NDA's on the ground that the products were no longer "new".

However characterized, the nub of what happened here was that through the actions of both USV and FDA, taken together, the NDA's were inactivated and the products involved became no longer "covered by an effective [new drug] application". Thus, plainly, the products satisfied the requirement of Clause (C) in § 107(c)(4) that they were not "covered by an effective [new drug] application" on October 9, 1962.

Nor, finally, does this conclusion make "surplusage" of Clause (C), as the court below suggested. The fact that an NDA'd product has become GRAS and no longer "new" does not, standing alone, automatically inactivate the NDA. Obviously there must be some further action which removes the product from new-drug regulation, before it can be found the product is no longer "covered" by an effective NDA. Here, however, FDA not only ruled that the products were GRAS, and thus "not new", but unambiguously acquiesced in USV's withdrawal of these products from new-drug regulatory procedures. FDA's own actions in connection with those of USV established that the products were no longer "covered". According to the District Court it was necessary for USV to show these additional facts in order to satisfy the criterion for exemption prescribed by Clause (C). Under no view of the statute as interpreted and applied by the District Court, therefore, can Clause (C) be considered surplusage.

3. *The Separate Error as to "Me-Too" Products.* Two of USV's bioflavonoid products had never been the subject of new drug applications, and had been marketed from the outset on the basis of USV's conclusion (and in one case FDA's as well) that they were not "new drugs". The opinion below "made clear" (Solicitor General's Petition for Certiorari, p. 16 n. 13, No. 72-555 (*Bentex*)) that "me-too" products generally are exempted by the "grandfather" clause, but then con-

cluded it would be inequitable to permit USV's "me-too" products a more generous treatment than their NDA'd predecessors. This result, the court conceded, "places [USV] in a less favorable position than that occupied by others who may have copied its product" and who, under the statute, are plainly entitled to "grandfather" protection. But that "inequity" inheres in the law, the court suggested, and "may only be redressed by Congress, not by the Courts under the guise of construction".

The Court of Appeals correctly analyzed the legal status of "me-too" products under the statute. But in its apparent unwillingness to allow USV's "me-too's" a more favorable disposition than the same company's pioneering NDA'd products, despite the protection clearly enjoyed by competing tag-along manufacturers, the court produced a result which does violence to the express terms of the statute and which, in fact, compounds inequity.

At the outset, the Court of Appeals acknowledged that USV's "me-too" products are "literally" exempt under the plain language of § 107(c)(4) since they had never been "covered" by an effective NDA, and the agency itself had contemporaneously ruled that prior to 1962 at least three of the products (including specifically one "me-too") were not "new drugs". Moreover, knowledgeable commentators recognized that such a result was "compelled by the literal language of the statute", and even FDA's own General Counsel had "conced[ed] that the position of his agency [to the contrary] was in considerable doubt".[29]

[29] App. A, *infra*, pp. 7a, 9a. Indeed, the recent scholarly commentary repeatedly cited by the court in its opinion asserts: "Ultimately, the issue of the status of 'me-too' drugs will have to be squarely faced, and the FDA interpretation of § 107(c)(4), holding that they follow the pioneer's fate, should be repudiated by the courts". *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown L. Journal 185, 206-07 (1971).

Yet the court would not accept the conclusion to which its own analysis led. To sustain the exemption for the "me-too" products, the court said (App. A, *infra*, p. 7a),

> "creates an inequitable result, provided the pioneer drug was NDA'd. In that event, the pioneer drug would be subject to withdrawal of marketing privilege *** whereas its copy would enjoy immunity from any such requirement under Section 107(c)(4)."

The court's escape from this dilemma of its own creation was through a novel—and, we submit, erroneous—application of the long-established doctrine that an NDA is "personal" to the manufacturer submitting the application and to the drug covered.

USV's new drug applications, being "personal to it", the court held (*id.*, p. 10a),

> "would cover all its products similar in formula, including those specifically described in its applications and all others like in formula. The similarity in formula between [USV's] NDA'd drugs and its 'me-too's' is stipulated. Under those circumstances, both the NDA'd and the 'me-too' drugs will be treated alike and neither can qualify for exemption * * *."

But this ruling—that an NDA radiates out to all similar products of the applicant—contravenes the vital second branch of the rule of personality: the NDA is "personal" not only to the manufacturer but to the specific drug as well. The NDA's approved for USV's original seven bioflavonoid products could not, as a matter of law, cover the two subsequently marketed products as to which no NDA's were ever filed.

FDA has never countenanced the marketing of a new dosage form or combination which was not itself GRAS, merely because the manufacturer had obtained

approval of an NDA for an earlier product involving the same principal ingredient. Nor has the agency ever previously made the argument that such new products were "covered" by the original NDA. Indeed, in 1957 FDA accepted and ruled upon supplemental NDA's covering several other new dosage forms of the product covered by USV's original NDA, without any suggestion that it viewed its action as superfluous. And, in the case of Bivam and Duo-CVP with Vitamin K, the agency plainly considered the products GRAS when introduced, hence "not new" drugs, hence never subject to preclearance through the NDA process, and hence never "covered" by an effective NDA.

We submit that the court below simply ignored the applicable law in an effort to mitigate an inequity of its own creation. That inequity is perceived cannot, however, justify departure from the scheme prescribed by Congress. As Judge Friendly wrote in *Pfizer, Inc.* v. *Richardson,* 434 F.2d 536, 542 (2d Cir. 1970), where the shoe was on the other foot, "a sufficient answer is the simple if not altogether satisfying one that Congress said so".

Indeed, to accept the conclusion of the Court of Appeals is to heighten, rather than mitigate, any inequity inherent in the law. Under the decision below:

— Pre-1962 NDA'd products which during that period became GRAS, would not be exempt;

— Even pre-1962 "me-too" products of the same manufacturer, although always GRAS, and never covered by an NDA, would not be exempt;

— Yet "me-too" products of other manufacturers, who had not invested the industry and resources required to obtain an NDA, but simply

piggy-backed on the effort of the pioneering manufacturer, would be exempt.

These anomalies can in fact be avoided, while still remaining faithful to the statute as enacted, by validating USV's primary contention as to the exempt status of its NDA'd products so as to produce a result which is equitable and consistent across the entire range of USV's bioflavonoid products. If, as we contend, the NDA'd products were not "covered" by effective NDA's on October 9, 1962—and this conclusion would seem to follow ineluctably from the course of dealings between FDA and USV during the years 1957-1962—then the pioneering NDA'd products are plainly qualified for the "grandfather" exemption of Section 107 (c)(4), along with the "me-too" products which were never "covered", and no inequity results.

But even if our position on the formerly NDA'd products is rejected, we submit, this Court should reinstate the applicability of the "grandfather" clause as Congress has written it to USV's "me-too" products, so as to avoid the even more arbitrary and illogical discrimination engrafted onto the statute by the court below.

CONCLUSION

Fair and effective application of the "grandfather" provision of the 1962 amendments to the Food, Drug, and Cosmetic Act has been seriously impaired by the decision of the Court of Appeals in this case. Unless reversed by this Court, the decision below will create great uncertainty and confusion both for the Food and Drug Administration in administering the statute and for manufacturers in complying with it. Further review is warranted not only by the impor-

tance of the issues and the desirability of obviating extensive and time-consuming further litigation in the lower courts, but by the clear errors of statutory construction and the manifest inequities reflected in the ruling below.

The petition for a writ of certiorari should therefore be granted.

Respectfully submitted,

ROBERT L. WALD,
SELMA M. LEVINE,
JOEL E. HOFFMAN,
Attorneys for Petitioner.

PHILIP ELMAN,
WALD, HARKRADER & ROSS,
Of Counsel.

October 30, 1972

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 71-1596

USV PHARMACEUTICAL CORPORATION, *Appellee,*

v.

ELLIOT L. RICHARDSON, Secretary of Health, Education, Welfare, and HERBERT L. LEY, JR., Commissioner of Food and Drugs, Food and Drug Administration, *Appellants.*

Appeal from the United States District Court for the Eastern District of Virginia, at Alexandria. Oren R. Lewis, District Judge.

(Argued December 8, 1971. Decided May 24, 1972.)

Before WINTER, RUSSELL and FIELD, Circuit Judges.

Howard S. Epstein, Attorney, Department of Justice, (Richard W. McLaren, Assistant Attorney General, Bruce B. Wilson, C. Coleman Bird, and Cheryl S. Karner, Attorneys, Department of Justice, and Peter Barton Hutt, Assistant General Counsel, Joanne S. Sisk, Richard S. Silverman, Attorneys, Food, Drugs, and Environmental Health Division, Department of Health, Education, and Welfare, on brief) for Appellants, and Joel Hoffman (Robert L. Wald, Selma M. Levine, and Wald, Harkrader, Nicholson and Ross on brief) for Appellee.

RUSSELL, Circuit Judge:

Unlike the drug manufacturers in *Bentex,*[1] this plaintiff

[1] *Bentex Pharmaceuticals, Inc.* v. *Richardson,* No. 71-1243 (4th Cir., appeal docketed March 11, 1971).

markets a line of citrus bioflavonoid drugs,[2] of which all but two were covered by NDAs issued at various times in 1955 and 1956. Like the plaintiffs in *Bentex,* however, it seeks by an action for declaratory judgment to secure the benefit of the exemption available under the "grandfather clause"[3] from the enlarged definition of a "new drug" included in the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act of 1938. The defendants, who are the Secretary of Health, Education and Welfare (hereinafter referred to as HEW) and the Commissioner of the Food and Drug Administration (hereafter referred to as Commissioner), urge that jurisdiction should be refused on two grounds: 1. Primary jurisdiction lies with HEW; and 2. Failure to exhaust administrative remedies. They, also, attack the right of the plaintiff to claim the exemption. The District Court sustained jurisdiction and, largely on the basis of a Stipulation of Facts, upheld plaintiff's right to the statutory exemption both for its NDA'd and its non-NDA'd drugs. We reverse.

The threshold question raised by the defendants and overruled by the District Court may be quickly disposed of. Under similar circumstances in *Bentex,* we sustained the right of the District Court to entertain an action for declaratory judgment. We reach the same result here. Since we dismiss the claim of the plaintiff for exemption on behalf of its drugs on substantive grounds, it is unnecessary to consider the additional objection that plaintiff has failed to exhaust administrative remedies.

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[2] "Bioflavonoid" is defined in Dorland's Illustrated Medical Dictionary, 2d Edition, as follows: "a generic term for a group of compounds which are widely distributed in plants and animals and which are concerned with maintenance of a normal state of the walls of small blood vessels." Stipulation of Facts, #4.

[3] Section 107(c)(4), Pub. L. 87-781 (1962), 21 U.S.C., 1972 Supplement, pp. 191-2.

The substantive issue posed by this action is the right of the plaintiff to the exemption provided by Section 107(c)(4) from the revised definition of "new drug" incorporated in the 1962 Amendments. In resolving that issue, we must differentiate, even as the "grandfather clause" itself does, between the plaintiff's drugs, which were covered by an "effective NDA",[4] and those, which were marketed without an NDA. The Act makes a distinction in "grandfather" rights between a drug marketed under an NDA[5] and one marketed without an NDA. In the case of a drug covered by a previously approved NDA, the 1962 Amendments required the Secretary to withdraw the approved NDAs if after notice and opportunity of hearing, the applicant failed to file substantial evidence[6] that the drug previously approved is both safe and effective.[7] For such drugs, however, a grace period or temporary "grandfather right" was granted. Under it, the manufacturer was given two years within which to develop his showing of effectiveness and, during this period, the Secretary was prohibited from withdrawing or suspending the previously granted NDA.[8] On the other hand, a non-NDA'd drug which met the criteria stated in Section 107(c)(4) was exempted permanently from the amended definition of "new drug" made by the 1962 Amendments and was thereby relieved of securing an approved NDA as a condition for marketing clearance. The statutory cri-

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[4] "Effective", as used in this phrase, means simply approved. Hagan, *Grandfather Protection Under the Drug Amendments of 1962*, 19 Food Drug Cosm. L. J., 119, p. 121.

[5] This is the term used to describe an approved preclearance application under Section 355.

[6] "Substantial evidence" is defined in the Act (21 U.S.C. 355 (d)).

[7] Section 355(e), 21 U.S.C.

[8] Section 107(c)(3)(B), 21 U.S.C., note foll. Section 321.

teria for this permanent "grandfather" exemption are stated as "any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined in Section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under Section 505 of that Act".

It is the contention of the plaintiff that all its drugs in question, both those previously NDA'd and those not, are protected by the permanent "grandfather clause" (i.e., Section 107(c)(4)). Because the statute seemingly makes a distinction between the two, it is proper to consider separately the two groups of drugs: i.e., those having NDAs and those without NDAs.

Taking up first plaintiff's NDA'd drugs: There is no dispute that such drugs met criteria (A) and (B), as set forth in the "grandfather clause", but the defendants seriously dispute the claim that they meet condition (C). Facially at least, this contention of the defendants seems unanswerable. These drugs are "covered by an effective application" or NDA, and are thus specifically barred by condition (C) from qualifying for exemption from the application of the effectiveness Amendments of 1962. The District Court found, however, that before "the day immediately preceding the enactment date", which was October 9, 1962, the previously granted NDAs had been effectively and practically withdrawn and that accordingly the drugs were not covered by an effective NDA on the crucial date of October 9, 1962. The error in this reasoning, however, is that it assumes that a manufacturer may effect a withdrawal of an effective NDA, either by a formal notice or by discontinuing compliance with the reporting requirements for NDA'd drugs. While an applicant may, during the pendency of his application, withdraw his application, he has no such right after approval of the application by the Secretary. At that point only the Secretary can with-

draw the approval. As one commentator has accurately summed up, "It is true that a manufacturer may withdraw a pending NDA. Sec. 21 C.F.R. sec. 130.8 (1971). However, no provision in the law permits a manufacturer to withdraw an effective NDA; only the FDA can do so through Section 505(e) procedure".[9] Prior to October 9, 1962, there was in this case no proceeding by FDA under Section 505(e) with reference to plaintiff's NDA'd drugs and there was accordingly no valid withdrawal of the plaintiff's effective NDAs, on or before the enactment date of the 1962 Amendments.

The plaintiff, though, presses another theory upon the basis of which it claims the previously issued NDAs are to be regarded as ineffective on October 9, 1962. Thus it argues that its pre-1962 NDA'd drugs became generally recognized as safe on or before October 9, 1962. So much the defendants seem to concede in the Stipulation of Facts submitted to the District Court. From this fact, it reasons that its NDA drugs ceased to be "new drugs" as defined in the Act, on or before October 9, 1962, and, ergo, its previously issued NDAs were no longer needed or "effective" on the critical date of October 9.[10] The difficulty with this argument, plausible though it may be, is that it would make surplusage of requirement (C) in the exemption statute. Thus, if a drug met the test set up in (B), that is, was generally recognized as safe on October 9, 1962, it would not be necessary, under the plaintiff's argument, to consider whether (C) was applicable or not. Such a construction of the exemption statute, under which a clearly stated condition to its application is to be treated as a nullity, offends the well-settled rule of statutory con-

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[9] Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185 at p. 198, n. 77 (1971).

[10] See Barth, *Following the NAS-NRC Effectiveness Review, What?*, 22 Business Lawyer, 1185, 1187 (1967).

struction that all parts of a statute are to be given effect if at all possible.[11] It is manifestly possible to give effect to the conditions enunciated in both (B) and (C). There are many drugs that satisfy both conditions, that is, are generally recognized as safe and effective and are being marketed without an approved NDA. There is nothing inconsistent in the two requirements. Moreover, condition (C) represented a limitation on the right to an exemption that the Congress clearly and unmistakably intended to apply. The Congress never intended that a drug being marketed under an approved NDA might qualify under the "grandfather clause." This is plain from the comment in the Conference Committee Report that the exemption was to apply "to existing labeling claims of drugs *that have never previously been subject to the new-drug procedure*". (Italics added.) H.R. Rep. 2526, 87th Cong., 2d Sess., p. 23. Moreover, the argument of the plaintiff would run counter to the principle that statutory exemptions, particularly as applied to statutes concerned with public health and safety, are to be strictly and narrowly construed.[12]

The plaintiff has, however, two drugs,[13] involved in this proceeding, which were generally recognized as safe and were[14] marketed as "old drugs" without an approved NDA on October 9, 1962. These drugs, as we earlier indicated, present separate problems from those drugs for which there are approved NDAs. They fall into the category of what are generally described in the trade as "me-

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[11] *Jarecki* v. *G. D. Searle & Co.* (1961) 367 U.S. 303, 307; *Ginsberg & Sons* v. *Popkin* (1932) 285 U.S. 204, 208.

[12] *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F. 2d 713, 718, cert. denied 385 U.S. 899.

[13] Duo-C.V.P. with Vitamin K Capsules and Bivam.

[14] Stipulation of Facts, Number 17.

too" drugs.[15] Such a drug, if generally regarded as safe on October 9, 1962, meets literally the criteria for exemption stated in the "grandfather clause". To sustain the exemption, however, creates an inequitable result, provided the pioneer drug was NDA'd. In that event, the pioneer drug would be subject to withdrawal of marketing privilege absent substantial evidence of effectiveness, whereas its copy would enjoy immunity from any such requirement under Section 107(c)(4). Most commentators, while admitting the incongruity of this result, justify it as one compelled by the literal language of the statute.[16] Their reasoning is similar to that of the Court in *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 542, where speaking to a somewhat illogical provision in this same Act, Judge Friendly said: "A sufficient answer is the simple if not altogether satisfying one that Congress said so."[17] The FDA itself has recognized the vexing problem presented by the "me-too" drug and has sought to resolve it by a change in its position on the scope and application of an NDA.

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[15] A "me-too" drug is generally defined as "one which is equivalent to another, pioneer drug, which preceded it on the market." Note, *Drug Efficacy and the 1962 Amendments,* 60 Georgetown L. Journal, 185, at p. 198, n. 78, (1971).

[16] See, Note, *Drug Efficacy and the 1962 Amendments,* 60 Georgetown L. Journal, 185, at p. 203 (1971):

> "Surely, me-too drugs never processed through the new drug procedures satisfy all the requirements of section 107 (c)(4)."

To the same effect is Hagan, *Grandfather Protection Under the Drug Amendments of 1962,* 19 Food Drug Cosm. L.J., 119, at pp. 125-6. D'Andrade, *The Effect of NAS-NRC Review on Me-Too and Post-'62 Drugs,* 25 Food, Drug, Cosm. L.J., 330, 334 (1970).

[17] This, of course, is not the only inequity in the Amendments. There are other inequities, as FDA freely conceded at a House Hearing before a Subcommittee of the Commission on Government Operations on Drug Efficacy, Part 2, 91st Cong., 1st Sess. (1969), pp. 384-5.

It is the contention of the FDA that an approved NDA covers not merely the marketing of the parent but also its "me-too" offsprings and for that reason the "me-too" drugs have been permitted to be marketed without an NDA. Accordingly, under this theory, the withdrawal of the approved NDA of the pioneer operates as a withdrawal of marketing rights for the "me-too", unless the latter, either individually or in conjunction with its pioneer, provides substantial evidence of effectiveness. This view has, however, been severely criticized and with considerable reason. It is, as one critic has observed, "at variance with the uniform position it (FDA) has taken over the years with regard to the nature of NDAs." This position, which is termed the "personal approach" holds that "Section 505 applies to drugs as individual articles, not as collective groups, and that each manufacturer of a new drug must file his own NDA." This critic concludes with the observation that it is "an unjustifiable exercise in semantics to say that a drug legally marketed without an NDA was 'covered' by the NDA of another manufacturer's drug.'"[18]

That the policy of FDA has heretofore been contrary to the position now taken by it is further illustrated by the circumstances under which at least one of the "me-toos" of the plaintiff began marketing. Prior to marketing Bivam, one of its "me-toos" similar in formula to other drugs previously NDA'd by it, the plaintiff inquired of FDA whether it was an "old drug" entitled to be marketed without an NDA. FDA, after reviewing its composition and labeling, advised the plaintiff it was a product "generally regarded as safe" (and thus an "old drug") and could be marketed without an NDA. There was no suggestion by the plaintiff that it sought to market this drug under any previous NDA granted one of its products nor did the FDA base its advice on that basis. Both the

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[18] Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 203, n. 111 (1971).

plaintiff and FDA assumed at that time that a "me-too" drug, which had become generally recognized as safe, was entitled to be marketed without an NDA; in short, that the qualification for marketing a "me-too" drug was general recognition of safety and not the NDA of its pioneer.

It would seem that the consistent construction of the Act by the FDA for thirty years[19] and a construction which accords with the literal language of the Act itself may only be changed by Congress itself.[20] In fact, the General Counsel of FDA, in testimony before a House Subcommittee Hearing on Drug Efficacy, Part 2 (91st Cong., 1st Sess., 1969) p. 375, expressed the wish that Congress would "pass" a clarifying amendment on this issue, conceding that the position of his agency was in considerable doubt.

But even if it be assumed that "me-too" drugs are generally entitled to Section 107(c)(4) protection, provided they were generally recognized as safe on October 9, 1962, that does not resolve the right of the plaintiff's "me-toos" to exemption. As has been pointed out, the reasoning on which "me-toos" are regarded as not covered by the

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[19] See, Hagan, *supra*, at p. 125:

> "Furthermore, the concept that new drug clearance by one manufacturer affects the rights of subsequent manufacturers is inconsistent with the established doctrine that new drug clearance is *personal* to the applicant, and does not embrace the drug *per se*."

[20] Cf., comment in Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal 185, at pp. 206-7 (1971):

> "Ultimately the issue of the status of me-too drugs will have to be squarely faced, and the FDA interpretation of section 107(c)(4), holding that they follow the pioneer's fate, should be repudiated by the courts. In that event the agency will undoubtedly ask Congress for new legislation to remedy the situation. In view of the obvious inequities in the present situation, this would seem to be the most desirable solution."

NDAs granted the manufacturers of their pioneers is that an NDA is regarded as "personal" to the manufacturer submitting the application and to the drug covered. But in this case, the "me-toos" are similar in formula and labeling to other drugs for which the plaintiff itself applied and obtained NDAs. It is true that, in the case of one drug at least, to which reference has already been made, plaintiff's "me-toos" were regarded as exempt, not because plaintiff had an approved NDA for a similar drug, but because FDA was of the opinion that it met the requirements for classification as an old drug. Nonetheless, it is the "personal" character of the NDA that has been deemed as the basis on which it is contended that the "me-toos" are not covered by the NDA granted another manufacturer, albeit the drugs involved may be similar. That reasoning manifestly cannot sustain a right of exemption in favor of plaintiff's "me-toos". The plaintiff's NDAs, being "personal" to it, would cover all its products similar in formula, including those specifically described in its applications and all others like in formula. The similarity in formula, between plaintiff's NDA'd drugs and its "me-toos" is stipulated. Under those circumstances, both the NDA'd and the "me-too" drugs will be treated alike and neither can qualify for exemption under the terms of Section 107(c)(4). It is recognized that this conclusion places the plaintiff in a less favorable position than that occupied by others who may have copied its product prior to October 9, 1962. That inequity is, however, inherent in the law and may only be redressed by Congress, not by the Courts under the guise of construction.

Reversed, with directions to enter judgment for the defendants.

REVERSED.

[Filed May 24, 1972]

APPENDIX B

Judgment

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 71-1596

USV PHARMACEUTICAL CORPORATION, *Appellee,*

v.

ELLIOT L. RICHARDSON, Secretary of Health, Education, and Welfare, Department of Health, Education, and Welfare, and HERBERT L. LEY, JR., Commissioner of Food and Drugs, Food and Drug Administration, *Appellants.*

Appeal from the United States District Court for the Eastern District of Virginia

This cause came on to be heard on the record from the United States District Court for the Eastern District of Virginia, and was argued by counsel.

ON CONSIDERATION WHEREOF, It is now here ordered and adjudged by this Court that the judgment of the said District Court appealed from, in this cause, be, and the same is hereby, reversed.

SAMUEL W. PHILLIPS
Clerk

[Filed July 5, 1972]

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 71-1596

USV PHARMACEUTICAL CORPORATION, *Appellee*,
v.
ELLIOT L. RICHARDSON, ET AL., *Appellants*.

Appeal from the United States District Court for the Eastern District of Virginia, at Alexandria.

Order

Upon consideration of appellee's petition for rehearing and of the suggestion for a rehearing en banc,

IT IS ORDERED, with the concurrence and approval of the panel and in the absence of a request for a poll of the entire court, as provided by Appellate Rule 35(b), that the petition be and it is hereby denied.

DONALD RUSSELL
United States Circuit Judge

APPENDIX D

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

Civil Action No. 4915-A

USV PHARMACEUTICAL CORPORATION, *Plaintiff*

v.

ELLIOT L. RICHARDSON, ETC., ET AL., *Defendants*

Order and Memorandum Opinion

This Court is of the opinion that the plaintiff's bioflavonoids here in question are exempted from the provisions of § 201(p) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301, et seq., as amended by P.L. 87-781, so long as such products are intended solely for use under conditions prescribed, recommended or suggested in the labeling thereof, as of October 9, 1962, and

IT IS SO ORDERED.

The controversy here turns on whether the plaintiff's bioflavonoids are "new drugs," within the meaning of 21 U.S.C. § 321(p), and thus subject to the efficacy review provisions of the amendment of 1962, or whether they are "old drugs" by reason of the "grandfather clause" in the 1962 amendment—§ 107(c)(4).

The Federal Drug Administration has determined that the plaintiff's bioflavonoids are "new drugs" and has called upon the manufacturer to document and establish their efficacy, as provided for in the 1962 amendment.

Rather than comply, or run the risk of criminal prosecution for non-compliance, the plaintiff brought this suit seeking pre-enforcement relief under 5 U.S.C. §§ 701-704

(Administrative Procedure Act) and 28 U.S.C. § 2201 (Declaratory Judgment Act). That such is proper to resolve conflicts of this type, see *Gardner* v. *Toilet Goods Association*, 387 U.S. 167 (1966).

The "grandfather clause," 107(c)(4) of the Act, reads as follows:

> "In the case of any drug which, on the day immediately preceding the enactment date [October 9, 1962], (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day."

If a statute grants exemptions to certain classes of products from its operation and a dispute arises as to whether or not a given product is entitled to such exemption, it is the Court's function—not the Administrator's—to determine whether or not such product is exempted. Thus, this Court has jurisdiction under the statutes above mentioned to hear and determine this controversy between the parties.

The Court's findings and conclusions follow.

The plaintiff has manufactured and sold its citrus line of bioflavonoid products in interstate commerce in substantial quantities from about 1955 to the present date.

Two of the plaintiff's products were never covered by effective new drug applications. The other seven were all covered at one time. These applications, however, were withdrawn prior to October of 1962. The plaintiff made that clear through its correspondence with the Fed-

eral Drug Administration. It then ceased compliance with the submittal of data and new labeling, as required by the Federal Drug Administration for products covered by effective NDAs.—The record further discloses that the Federal Drug Administration advised the plaintiff in writing that its products covered by NDAs 11474 and 11475 were not new drugs—and it was stipulated that the compound in these two products is identical to the bioflavonoid compound in plaintiff's other products and that the recommended uses of all of the CVP products are essentially the same.

From this evidence, the Court finds that none of the plaintiff's bioflavonoid products in question were covered by an effective NDA as of October 9, 1962.

Whether the plaintiff's bioflavonoids are "new drugs" within the meaning of § 201(p) of the basic Act (codified as 21 U.S.C. § 321 (p)) is the key question for determination here.

> "The term 'new drug' means—
>
> "(1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ."

The word "safe" as used in the basis Act refers to the health of man or animal [1]—efficacy was not added until the 1962 amendment.

Measured by the standard employed by the Federal Drug Administration prior to the effective date of the 1962 amendment, the Court finds that the plaintiff's bioflavonoids were "safe," as that word was then understood.

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[1] 21 U.S.C. § 321(u).

All of the expert witnesses, including those called by the Government, were of the opinion that the plaintiff's bioflavonoids were innocuous when taken by anyone in any condition.

All agreed they were non-toxic and harmless per se in that a normal individual given such a product would not develop an adverse reaction, and were safe for use under the conditions prescribed, recommended or suggested in the labeling—that is, abnormal capillary permeability and fragility—The plaintiff's experts went further—They said the plaintiff's bioflavonoids were not only safe but were quite effective, when used as recommended, in certain types of capillary bleeding.

The Government's experts contend that the safety of a drug can only be determined by its efficacy—a "safe drug" becomes "unsafe" when used in place of the proper drug—the harm comes from the failure to use the best known drug for the treatment of the ailment complained of. This may or may not be so under the 1962 amendment—the Court does not determine that question here.

This decision is limited solely to the determination of whether the plaintiff's drugs are entitled to the exemption set forth in § 107(c)(4) of the Act.

The Clerk will send a copy of this order and memorandum opinion to all counsel of record.

/s/ OREN R. LEWIS
United States District Judge

April 1, 1971

APPENDIX E

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA

Civil Action No. 4915-A

USV PHARMACEUTICAL CORPORATION, *Plaintiff*,

v.

ELLIOT L. RICHARDSON, ET AL., *Defendants*.

Motion for Clarification of Order and Memorandum Opinion

Plaintiff USV Pharmaceutical Corp. respectfully requests the Court's guidance in interpreting the order and memorandum opinion filed herein on April 1, 1971. Specifically, we ask the Court to confirm that in its order and opinion the Court has found:

1. That plaintiff's bioflavonoid products here in question are, today, not "new drugs" under the pre-1962 statutory definition of the term, and therefore exempt from the "new drug" provisions of the statute.

2. That on October 9, 1962 plaintiff's bioflavonoids were, and are today, generally recognized by qualified experts as safe for their intended uses, as the word "safe" was then understood.

Respectfully submitted,

THOMAS MONCURE
Thomas Moncure
121 South Royal Street
Alexandria, Virginia 22314

SELMA M. LEVINE
Selma M. Levine
JOEL E. HOFFMAN
Joel E. Hoffman
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1320 Nineteenth Street, N. W.
Washington, D. C. 20036

April 12, 1971

APPENDIX F

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

Civil Action No. 4915-A

USV PHARMACEUTICAL CORPORATION, *Plaintiff*,

v.

ELLIOT L. RICHARDSON, ET AL., *Defendants*.

United States Court House
Tuesday, May 4, 1971
10:00 a.m.

BEFORE: Hon. Oren R. Lewis,
Judge, United States District Court.

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The Court: So that we will get the record clear,—I've got many things to do, and this isn't one of them—on page 4 you have asked me to confirm that I found No. 2 that were and are today generally recognized as safe for their intended uses as the word "safe" was then understood. I believe that I said that when I said that the court finds that these bioflavonoids were safe as that word was then understood.

Mr. Hoffman: That is fine.

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The Court: Now, as your No. 1, you asked me that they are exempt from the new-drug provisions of the statute.

Mr. Hoffman: That is correct, your Honor.

The Court: Well, I couldn't have found that any better in your ways when I made it very clear that that is all I was doing.

Mr. Hoffman: That is right, your Honor.

The Court: I held that this decision, the last paragraph is limited solely to the determination of whether the plaintiff's drugs are entitled to the exemption set forth in the statute; isn't that right? And I held that they were.

Mr. Hoffman: That is right, your Honor.

The Court: Now, I limited it to the exemption.

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Page 14:

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The Court: The court clearly intended to hold that they were exempted by the grandfather clause. Now, that is all period.

Mr. Hoffman: Exempted by the grandfather clause from new-drug regulation.

The Court: That is correct, and that is all I held.

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APPENDIX G

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO., *Appellants*,

v.

ELLIOT P. RICHARDSON, Secretary of the Department of Health, Education and Welfare and CHARLES C. EDWARDS, Commissioner of the Food and Drug Administration, *Appellees*.

Appeal from the United States District Court for the District of South Carolina, at Greenville. Robert W. Hemphill, District Judge.

(Argued December 8, 1971 Decided May 23, 1972.)

Before WINTER, RUSSELL and FIELD, Circuit Judges.

GEORGE F. TOWNES (Sol E. Abrams on brief) for Appellants, and CHARLES R. MCCONACHIE, Attorney, Depart-

ment of Justice, (Will Wilson, Assistant Attorney General, John L. Murphy, Chief, Administrative Regulations Section, William W. Goodrich, Assistant General Counsel, Food, Drugs, and Environmental Health Division, Robert N. Anderson, Attorney, United States Department of Health, Education and Welfare, and Howard S. Epstein, Attorney, Department of Justice, on brief) for Appellees.

RUSSELL, Circuit Judge:

This appeal turns on a construction of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1962.[1] 21 U.S.C. 301, *et seq.* This statute requires pre-marketing approval and clearance of any "new drug" by the Secretary of Health, Education and Welfare.[2] The term "new drug" is defined as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective

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[1] There was an earlier Food and Drug Act of 1906. 34 Stat. 768 (1906). It did not provide for any pre-marketing review of the safety of drugs. The sulfanilamide episode in 1938 prompted the enactment of the Federal Food, Drug and Cosmetic Act of that year to replace the earlier Act and to provide, *inter alia*, for such pre-marketing review of "new drugs". See C. W. Dunn, *Federal Food, Drug and Cosmetic Act-A Statement of Its Legislative Record*, pp. 1316-27 (1938). The fears generated by the thalidomide tragedies gave the impetus for the Amendments of 1962. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, 185 at p. 191, n. 45 (1971).

[2] Section 355(a), 21 U.S.C.

The actual approval of a "new drug" under the Act is normally processed by the Food and Drug Administration (FDA) in the Department of Health, Education and Welfare (HEW), and the approvals, when granted, are generally referred to as New Drug Approvals (NDAs). FDA, when used herein, refers to the Food and Drug Administration, and NDA is intended to describe an approval by FDA of a "new drug" application under the Act.

for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * *."[3] From a denial of a pre-marketing approval or a withdrawal of a previously given approval, an appeal, originally to the District Court, now to the Circuit Court of Appeals, is authorized.[4] Drugs which do not fit the definition of a "new drug" do not require FDA clearance for marketing. There is no provision in the Act for administrative determination whether a particular drug is a "new drug" nor for any right of appeal from any such determination. The FDA sometimes offers to render "informal advice" as to whether it considers a product a "new drug" but it uniformly designates such opinion "advice."[5] Accordingly, the responsibility for determining whether its product is a "new drug," requiring pre-marketing clearance by FDA, rests on the manufacturer, who must act at its peril.[6] If it makes an incorrect determination and seeks to market without FDA clearance a drug meeting the definition of a "new drug," it lays itself open to drastic judicial procedures that may be invoked by FDA, i.e.: The product may be seized in an *in rem* action instituted by the Government;[7] its sale may

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[3] Section 321 (p)(1), 21 U.S.C.

See, also, *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C.Md. 1967) 274 F.Supp. 443, 445, n. 2:

> "The statutory definition of the phrase 'new drug' controls this case, regardless of any other meaning attributable to the phrase or to the word 'new' by common understanding or other authority."

[4] Section 355(h), 21 U.S.C.

[5] 21 C.F.R. 130.39.

[6] Cf. *United States* v. *Dotterweich* (1943) 320 U.S. 277, 281, where, speaking of the Act of 1938, the Court said:

> "In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."

[7] Section 334, 21 U.S.C.

be enjoined in an action begun by the Government;[8] in addition, the manufacturer may be subjected to criminal action.[9] All these remedies must be prosecuted in the District Court and the role of the Secretary is that of plaintiff or prosecutor. The Act thus establishes two forums for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined "new drug," with right of appeal from a denial of approval, or withdrawal of a previous approval, to the District Court, later changed to the Court of Appeals; the other is judicial and is intended to make effective and give strength to the requirement that "new drugs" be cleared as safe before marketing by providing the Government with certain potent judicial remedies, *available exclusively in the District Court.*

Under the 1938 Act, a new drug was one "not generally recognized by experts * * * as safe for its intended use." The Amendments added "effectiveness" as well as "safety" to the definition. Simply stated, the change effected by the Amendments was that, whereas prior to the 1962 Amendments a drug which was generally recognized as safe was not a "new drug," the Amendments defined a drug as "new" if it were not generally recognized as both safe *and effective.* Furthermore, they replaced the provision for automatic approvals of applications not disapproved within a fixed time with a requirement of a positive act of approval on the part of FDA.[10] They proceeded to provide that the Secretary must find as a basis for clearance of a new drug not only safety but "substantial evidence" of effectiveness, "consisting of adequate and well-controlled investigations, including clinical investigations, by experts

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[8] Section 332, 21 U.S.C.

[9] Section 333, 21 U.S.C.

[10] Section 355(e), 21 U.S.C.

qualified by scientific training and experience to evaluate the effectiveness of the drug involved." The applicability of these amendments, including the revised definition of "new drug" to drugs already marketed, either under previously issued NDAs, or as "old drugs" requiring no FDA approval, was carefully spelt out in the Amendments and certain "grandfather rights" were granted. For all previously NDA'd drugs, the Amendments conferred a grace period of two years after the effective date of the Amendments within which to prepare evidence to satisfy the new requirement of efficacy added by the revised definition of "new drug"; during that "transitional" period no revocation or withdrawal of approval because of a lack of substantial evidence of efficacy of such drugs was permitted.[11] For a drug, however, which on the day prior to the enactment of the Amendments was (1) being "commercially used or sold in the United States," (2) "was not a new drug as defined by" the pre-Amendment statute and (3) "was not covered by an effective (new drug) application, • • •" "on the day immediately preceding the enactment date" of the Amendments, there was a permanent exemption from the efficacy provisions of the Amendments so long as the drug's labeling remained the same.[12] In summary, these provisions required that, "Those drugs which had obtained effective NDAs must be proven efficacious after two years; those which had not need never be proven

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[11] Section 107(c)(3), P.L. 87-781, Section 321, Supplement 1972, 21 U.S.C.

[12] Section 107(3)(4), P.L. 87-781, Section 321, 1972 Supplement, 21 U.S.C.; see, also, *Tyler Pharmacal Distrib. Inc.* v. *U. S. Dept. of Health, E. & W.* (7th Cir. 1969) 408 F.2d 95, 99.

It should be noted that Section 321(p)(1) provides a "grandfather clause" applicable to pre-1938 drugs. This clause is not relevant to this action, which is concerned with drugs introduced between 1938 and 1962, and the subsequent references to "grandfather clause" in this opinion are to section 107(c)(4).

efficacious so long as they had become safe prior to the 1962 Amendments." [18]

The "grandfather clause" set forth in Section 107(c)(4) simply continues for the products satisfying its criteria the pre-1962 definition of a "new drug." Its effect is to assure that a drug which was generally recognized by qualified experts as safe for the purposes recommended for its use on October 9, 1962, need not be NDA'd as *effective* under the new requirements for the issuance of an NDA as a "new drug." But any drug, whether requiring an NDA or not, whether a "new drug" or an "old drug," is subject to the misbranding provisions of the Act and may be proceeded against on that basis. A false claim of either safety or effectiveness constitutes misbranding, rendering a drug subject to both civil and criminal penalties. *United States* v. *Article of Drug Labeled Decholin* (D.C.Mich. 1967) 264 F. Supp. 473, 482-3; *United States* v. *Lanpar*

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[18] Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, p. 196 (1971).

See, also, *United States* v. *Allan Drug Corp.* (10th Cir. 1966) 357 F.2d 712, 719, note 9, quoting from the Supplemental Report of the Senate Committee on Drug Amendments of 1962, as set forth in the notes to Section 321, 21 U.S.C.:

> "Thirdly, in the case of a drug on the market which was never subject to the new-drug procedure before, the amendments to the new definition relating to drug effectiveness would not apply to existing labeling claims."

In the Conference Report of the House Managers on the Amendments, it was stated that the Amendments included "the Senate language providing with respect to existing label claims of drugs that have never previously been subject to the new-drug procedure substantially the same savings provisions as the corresponding provision of the House bill (Section 197(d))." *U.S. Code Congressional and Administrative News*, 87th Congress, 2d Session (1962), p. 2932. Again, in H. R. Rep. #2526, p. 23, it is stated that the exemption granted by the "grandfather clause" applies "to existing claims of drugs that have never been subject to the new-drug procedure".

Company (D.C.Tex. 1968) 293 F. Supp. 147, 153-4.[14] Accordingly, in *United States* v. *Guardian Chemical Corporation* (2d Cir. 1969) 410 F.2d 157, a drug manufacturer was acquitted of a charge of marketing a "new drug" without an NDA, but was convicted under a separate count of the indictment charging misbranding. "Thus," as one commentator has aptly stated, "the amplications of the FDA's authority (as granted by the 1962 Amendments) is (was) not due to the absence of power to proceed against ineffective drugs, but rather to authorize the exercise of that power at the initial stage, that is, *before* marketing, and also to shift the burden of proof to the applicant." Jurow, *The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments*, 19 Food, Drug, Cosmetic Law Journal, 110, at p. 116 (1964).[15]

The plaintiffs, manufacturers of a prescription drug containing pentylenetetrazol and nicotinic acid, claim the

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[14] See, also *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F.2d 536, 548:

> "A good case could certainly be made that quite apart from this, the 'efficacy' of a drug is necessarily related to the use recommended."

[15] See, also Senate Report #1744, *U.S. Code Congressional and Administrative News*, 87th Cong., 2d Sess. (1962), pp. 2892 and 2893, where, in justifying the Amendments, it is stated:

> "* * * where a drug is essentially innocuous, it (FDA) must clear the drug despite the fact that its claim of effectiveness is not borne out by the evidence. In such cases the Food and Drug Administration may proceed against the drug manufacturer by seizure of the drug for misbranding. However, the Department believes that the manufacturer should satisfy the Food and Drug Administration that his product is effective for the purposes claimed before it is marketed. * * * No question of safety is involved, and the Food and Drug Administration presently has ample power, including seizure, to proceed against any safe drug for which unsupported claims of effectiveness are made."

protection of the "grandfather clause" included in Section 107(c)(4) for their products and that contention represents the substantive issue in this case. It is undisputed that plaintiffs had marketed their product commercially for many years prior to and on October 9, 1962,[16] without an NDA under the claim that it was not a "new drug" within the definition of the Act, and therefore required no NDA. Such claim was supported, it is asserted, both by previous informal advice of the Secretary and by the general recognition of the safety of such product by "experts qualified by scientific training and experience" to make such evaluation. The defendants, the Secretary of HEW and the Commissioner of Food and Drugs, in their brief, concede that "Over the years since 1938" and until 1968, the Food and Drug Administration had given the opinion that certain pentylenetetrazol combinations similar to those of the appellant were not "new drugs."[17] Moreover, the District Court observed in its opinion that there was "no contention (by the FDA) that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs." On this basis, the plaintiffs contended that they met exactly the criteria established for exemption from the requirements of general recognition by qualified experts of the effective-

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[16] This was the day "immediately preceding the enactment date" of the Amendments of 1962.

[17] It is, of course, axiomatic that such opinions or advice can create no estoppel against the Government. *AMP, Incorporated* v. *Gardner* (D.C.N.Y. 1967) 275 F.Supp. 410, 412, n. 1, aff. 389 F.2d 825, cert. den. 393 U.S. 825, reh. den. 395 U.S. 917. The most that can be claimed for such opinions is that they lend color and good faith to the plaintiffs' claims. FDA not only has the right but is obligated to change its opinion if it learns its prior position was erroneous. *United States* v. *60 28-Capsule Bottles, More or Less, etc.* (D.C.N.J. 1962) 211 F.Supp. 207, 215, aff. 325 F.2d 513.

ness of their products as provided in the permanent grandfather section of the 1962 Amendments.

Prior to the filing of this action, however, the defendants withdrew their advice that products such as those distributed by the plaintiffs were "old drugs" and contended that such products did not qualify for exemption under the "grandfather clause," Section 107(c)(4). The basis for this contention was the claim (1) that these drugs were not generally recognized by qualified experts as safe as of the effective date of the Amendments of 1962 and (2) that they were "me-too" drugs, whose marketability without FDA clearance depended in turn on the NDAs granted the basic drug, and for that reason must be regarded as drugs covered by an effective NDA on the effective date of the Amendments.[18] Faced with this threat, the plaintiffs began

[18] The defendants assert that three "new drug" applications filed by other manufacturers and earlier approved by the FDA covered drugs similar in every particular to those marketed by the plaintiffs. Proceedings for withdrawal of the approval of such "new drugs" had been begun by FDA in advance of the filing of this action. In fact, such proceedings to a large extent prompted this action. It is the contention of the defendants that the withdrawal of what they describe as "the primary NDAs" operates to remove the marketability from what they assert are the "me-toos" or non-NDA'd drugs which are similar to other drugs which have secured effective NDAs. The plaintiffs deny that their drugs are like those previously NDA'd. They argue that those NDA'd products, unlike theirs, are intravenously administered or are a compound containing, in addition to the components of plaintiffs' drugs, reserpine. Such changes in formula or method of administering vitiated any claim by their manufacturers that they were marketing an old drug and required an approval as a new drug. The plaintiffs assert their drugs are not subject to any such disability. These, however, are questions of fact not relevant to the simple question of jurisdiction presented by this appeal and may be inquired into on remand. Even if the products of the plaintiffs be deemed "me-too" drugs (i.e., simply "a copy of a pioneer drug which preceded it on the market"), it is by no means clear that they do not "meet the requirements for section 107(c)(4) protection" and the argument of the Government to the con-

this action for a declaratory judgment sustaining their right to exemption from proof of the effectiveness of their product and for injunctive relief awaiting the disposition of their claim for exemption. The defendants directed against the complaint a motion to dismiss or for summary judgment, which, in essence, (1) asserted primary jurisdiction in the Secretary to determine whether the products of the plaintiffs met the requirements for exemption under Section 107(c)(4), particularly whether they were "new drugs," requiring pre-marketing approval under the Act, (2) denied the propriety of a declaratory judgment action, and (3) claimed that the products of the plaintiffs were "new drugs" which did not qualify for exemption under the "grandfather clause."

The District Court sustained the right of the plaintiffs to maintain a suit for a declaratory judgment and the jurisdiction of the Court in such action to determine judicially whether the products of the plaintiffs were "new drugs," on the effective date of the Amendments, and whether they were or were not entitled to the benefits of the "grandfather clause."[19] However,—and this is the nub of the controversy

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trary has been described as "lacking in merit." See, Note, *Drug Efficacy and the 1962 Amendments,* 60 Georgetown Law Journal, 185 at p. 203-207 (1971); Hagan, *Grandfather Protection under the Drug Amendments of 1962,* 19 Food Drug Cosmetic Law Journal 119, at p. 125 (1964).

[19] In support of the right of the plaintiffs to maintain a suit for declaratory judgment, the District Court relied on *Abbott Laboratories* v. *Gardner* (1967) 387 U.S. 136 and the companion case of *Toilet Goods Assn.* v. *Gardner* (1967) 387 U.S. 158. Additional support for such right is found in *AMP, Incorporated* v. *Gardner, supra; Durovic* v. *Richardson* (D.C. Ill. 1971) 327 F.Supp. 386; *Lemmon Pharmacal Co.* v. *Richardson* (D.C. Pa. 1970) 319 F.Supp. 375. The right of the Court to determine the applicability of the "grandfather clause" is equally clear and has been sustained in *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F.Supp. 443, 445; and *United States* v. *Article Consisting of 36 Boxes, etc.* (D.C. Del. 1968) 284 F.Supp. 107, 112, n. 13, aff. 415 F.2d 369.

between the parties on this appeal—it concluded that the Secretary had concurrent jurisdiction to determine whether plaintiffs' products were "new drugs," requiring pre-marketing clearance, and that, because of the greater expertise of the Secretary in the field, it deferred to the Secretary's assumed jurisdiction to determine whether the drugs of the plaintiffs came within the exemption provided by the "grandfather clause." It enjoined any action against the plaintiffs and their products until the plaintiffs had been accorded a hearing before the Secretary on the issue of the qualifications of these drugs for protection under the "grandfather clause." It is the conclusion of concurrent jurisdiction in the Secretary and deference to that assumed concurrent jurisdiction from which the plaintiffs have prosecuted this appeal.

The defendants, on the other hand, have not cross-appealed and have accordingly acquiesced in the decision of the District Court that the action is properly maintainable as a declaratory judgment proceeding under Section 2201, 28 U.S.C. and that the District Court has jurisdiction over the substantive issue in this case, i.e., whether plaintiffs' products are "new drugs," as defined in the Act. The question in the case is thus whether the Secretary has concurrent jurisdiction to determine whether a drug is a "new drug" under the Act or whether that issue is cognizable only in the District Court. Contrary to the conclusion of the District Court, we conclude that the Act confers no such jurisdiction on the Secretary and, therefore, no basis for any deference by that Court to the concurrent jurisdiction of the Secretary.

The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or a new drug. It may, in its prosecutorial role, reach a conclusion that a product being marketed is a "new drug" requiring pre-marketing approval; but that opinion is not adjudicatory, it is only the basis on which the FDA, as the

prosecutor or initiator of either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that Court to determine, among other issues, whether the drug challenged is a "new drug." There is manifestly no provision in the Act for an administrative proceeding before the Secretary to compel the filing of a "new drug" application or to halt the marketing of a drug for which there is no approval by the Secretary. It is not without significance that, so far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. The only occasions on which he has sought to assert such jurisdiction has been as an element in his defense to a declaratory judgment action.[20] Moreover, when FDA undertook its new responsibilities under the 1962 Amendments, it sought merely to review "the efficacy of *all new drugs that had been cleared*, for safety only, between 1938 and October 10, 1962" (Italics added) and enlisted the services of the National Academy of Sciences—National Research Council for this limited task. It did not assert the right to review, or assume the burden of reviewing, for efficacy, drugs such as those involved here, which had been commercially marketed on the basis of a general recognition of safety without an effective NDA as of the effective date of the 1962 Amendments. It, thus, recognized that its adjudicatory rights extended merely to the approval, or the withdrawal of approval,[22] of a drug embraced in a "new drug" application that had been ap-

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[20] See, *Hynson, Westcott & Dunning, Inc.* v. *Richardson* (Civ. No. 21112, D. Md., decided 9/16/70); and *Ciba Corp.* v. *Richardson* (Civ. No. 1210-70, D. N.J., decided 3/10/71); but cf., *Lemmon Pharmacal, supra.*

[21] See *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F.2d 536, 539, and 31 F.R. 9426.

[22] The authority of the Secretary to withdraw an approval of any "new drug" application filed under the Act of 1938 after hearing is specifically granted by Section 355(e), 21 U.S.C.

proved. This confirms the conclusion that the halting of the marketing of a drug, for which there is no NDA, may not be by administrative action but must be by an injunction or *in rem* seizure proceeding, in which the Secretary appears, not in a judicial but in a prosecutorial role.[23] Those are the procedures prescribed and available to the Government under the Act.[24] The Secretary, it is true, has offered to provide "advice" on whether a product meets the qualification of an old drug but he categorizes his action in such instances as merely "advice" and makes no claim of finality therefor. Nor is there, as we have already observed, any provision for judicial review of such "advice."[25] The only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a "new drug" application.[26] That this is so follows from the limitations placed by the Act on judicial review of the decisions of the Secretary. The Secretary himself asserted, shortly after the enactment of the 1962 Amendments, in *Turkel* v. *Food and Drug Administration, Dept. of H.E.W., supra,* at p. 845, that the Act "grants a

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[23] Of course, in a proper case the Government may also institute criminal proceedings in the District Court. See Section 333, 21 U.S.C.

[24] Cf. *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F.2d 713, 718, cert. den. 385 U.S. 899, in which the Secretary is quoted to the effect that, " 'As to drugs already on the market that have never been subject to the new-drug procedure but are not generally recognized as effective, the burden remains on the Government to prove *in court,* insofar as unchanged labeling claims are concerned, they do not have their claimed effect. If the labeling claims are changed, however, these must be approved under the new-drug procedure.' " (Italics added.)

[25] See *Turkel* v. *Food and Drug Administration, Dept. of H.E.W* (6th Cir. 1964) 334 F.2d 844, 846, cert. denied 379 U.S. 990, rehearing denied 380 U.S. 927: "The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute."

[26] Section 355(b), 21 U.S.C.

right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application." In keeping with the Secretary's contention as to the extent of his adjudicatory powers, the Court in that case held that the right of appeal from an order of the Secretary "applies only to an order of the Secretary refusing or withdrawing approval of an application for sale and distribution of a new drug" (at pp. 845-6). It is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed. Yet this is the unusual situation that would be presented if the Secretary were held to have jurisdiction to adjudicate whether a drug meets the statutory criteria of a "new drug."[27]

The District Court, in finding concurrent jurisdiction, held that "This grant of authority to approve or withhold approval of new drug application, * * * necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which required an approved new drug application for lawful interstate shipment." This reasoning assumes that an application for approval by the Secretary under the Act poses as its initial issue whether the product is a new drug. No such issue is posed by the application. The very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a "new drug"; otherwise, there would be no reason to file the application. As a matter of fact, in the prescribed form of application, the applicant describes his product as "new drug." 21 C.F.R. 130.4. The applicant makes the determination whether his product is a "new drug" and whether he must file for pre-marketing clearance by the Secretary. And when filed, the application puts in issue only one question: Is the article safe and effective? That and that alone is the issue to be

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[27] Cf. *Abbott Laboratories* v. *Gardner* (1967) 387 U.S. 136, at p. 140.

considered by the Secretary in connection with an application for approval filed by a manufacturer under Section 355(d), 21 U.S.C. That issue is quite different from that presented when there is an issue whether a drug fits the statutory definition of "new drug" in the Act. The criterion for ascertaining whether a product is within the statutory definition of "new drug" under the Act is not safety and effectiveness *per se*, which, as we have observed, is the issue before the Secretary in connection with application for approval of a "new drug," but "whether the government has shown by a preponderance of the evidence that the 'drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof.' "[28] That is an issue that must be and is resolved, sometimes with, and at other times without a jury, in practically every injunctive, seizure, or criminal proceeding under the Act. See, for instance, *United States* v. *Articles of Drug Labeled "Quick-O-Ver," supra*; *United*

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[28] *United States* v. *Articles of Drug Labeled "Quick-O-Ver", supra*, at pp. 445-6.

See, also:

AMP, Incorporated v. *Gardner, supra*, at p.831:

"But the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness—if there is not, the products must be submitted to the Secretary of Health, Education and Welfare for a determination as to safety, adequacy of testing, etc."

United States v. *Article of Drug, etc.* (5th Cir. 1969) 415 F.2d 390, 392:

"Both sides agree that the nature of expert opinion about Furestrol, and not its actual safety or effectiveness, is the ultimate fact issue."

Cf., *United States* v. *Seven Cartons, More or Less, etc.* (7th Cir. 1970) 424 F.2d 1364, 1365.

States v. *41 Cases, More or Less* (5th Cir. 1970) 420 F.2d 1126, 1128; *United States* v. *Article of Drug, etc., supra,* at p. 392; *United States* v. *Article . . . Consist. of 216 Carton* (2d Cir. 1969) 409 F.2d 734, 742; *United States* v. *Article Consisting of 36 Boxes, etc., supra,* at p. 113; see, also, *United States* v. *Article of Drug, etc.,* (D.C.Md. 1971) 331 F. Supp. 912, 915-7. That was one of the issues resolved in the declaratory action of *Lemmon Pharmacal Co.* v. *Richardson, supra.*[29] It is manifestly a justiciable issue and the plaintiffs are entitled to a judgment on that issue by the Court, which alone has the jurisdiction to resolve it. In the absence of any statutory review proceedings within which they may assert their claim of exemption, the plaintiffs are not to be compelled to proceed at their peril, subject to the possibility of both civil and criminal penalties, but are entitled to seek relief by way of a declaratory judgment action. The District Court should accordingly have retained jurisdiction and proceeded to determine whether the plaintiffs' drugs met the criteria for exemption under Section 107(c)(4). We deem it premature for us to consider at this stage whether plaintiffs' products meet such criteria. That issue was not developed in the record before, or ruled on by, the District Court.[30] Upon remand, the issue can be considered by the Court in the light of the record that may be made by the parties.

REMANDED, WITH DIRECTIONS.

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[29] In discussing this case, the commentator in 60 Georgetown Law Journal, p. 199, note 87, says:

> "In *Lemmon Pharmacal,* the Court, while noting that determining safety and efficacy would normally be within the primary jurisdiction of the agency, concluded that the question of section 107(c)(4) protection was properly before it."

[30] See *United States* v. *Article Consisting of 36 Boxes etc., supra,* at p. 113.

APPENDIX H

Notice: This opinion is subject to formal revision before publication in the Federal Reporter or U.S.App.D.C. Reports. Users are requested to notify the Clerk of any formal errors in order that corrections may be made before the bound volumes go to press.

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 24,900

USV PHARMACEUTICAL CORPORATION, *Petitioner*

v.

SECRETARY OF HEALTH, EDUCATION & WELFARE and COMMISSIONER OF FOOD & DRUGS, *Respondents*

Petition for Review of an Order of the Commissioner of Food & Drugs

---

Decided August 14, 1972

Mr. Joel E. Hoffman, with whom *Messrs. Robert L. Wald*, *Stephen M. Truitt* and *Miss Selma M. Levine* were on the brief, for petitioner.

Mr. Howard S. Epstein, Attorney, Department of Justice, with whom *Messrs. John L. Murphy*, Chief, Administrative Regulations Section, Department of Justice, *William W. Goodrich*, Assistant General Counsel, and *Joanne S. Sisk*, Attorney, Department of Health, Education and Welfare, were on the brief, for respondent.

Before ROBINSON, ROBB and WILKEY, *Circuit Judges*.

ROBB, *Circuit Judge:* The petitioner, USV Pharmaceutical Corporation (USV), is engaged in the manufacture and marketing of a line of citrus bioflavonoid drugs known as

CVP.[1] The petitioner challenges an order of the Commissioner of Food and Drugs [2] withdrawing approval of three New Drug Applications held by USV for these drugs. The order was issued pursuant to section 505(e) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(e) (1970), and its effect is to make the interstate distribution of the drug illegal. 21 U.S.C. §§ 331, 355. The Commissioner says that his order is supported by his finding that there is a lack of substantial evidence, as that term is defined in the Act, 21 U.S.C. § 355(d), that the drugs will have the effectiveness claimed for them. The petitioner counters that the order is invalid because of substantial defects in the proceedings upon which it is based. Reviewing the matter pursuant to 21 U.S.C. § 355(h), we are constrained to agree with the petitioner.

Under the statutory scheme the Commissioner approves or disapproves a drug upon the basis of what is known as a New Drug Application (NDA) submitted by the person proposing to introduce the drug into interstate commerce. In 1956 and 1957 three NDAs for the petitioner's CVP drugs were approved by the Commissioner pursuant to the Federal Food, Drug and Cosmetic Act of 1938, 52 Stat. 1041, 1052, 21 U.S.C.A. §§ 321(p), 355 (1961). Under this statute drug approval was granted if the sponsor submitted proof establishing that the drug was safe for its intended use. No determination of the drug's effectiveness for its

---

[1] CVP is the trade name under which the petitioner markets drugs containing citrus flavonoid compound, a derivative of citrus fruit pulp and peel, and vitamin C, with and without vitamin K. CVP is a bioflavonoid, a generic term which may refer not only to citrus flavonoid compounds but also to any of its separate components. These drugs are recommended by the petitioner for the control of abnormal capillary premeability and a number of serious blood disorders.

[2] The Commissioner acted under authority delegated by the Secretary of Health, Education and Welfare. 21 C.F.R. § 2.120 (1971).

prescribed uses was required. In 1962, however, the relevant sections of the statute were amended to require a showing by a drug sponsor that a drug was both safe and effective for its prescribed uses. Act of October 10, 1962, 76 Stat. 781-783, 784, 785, 21 U.S.C. § 355. Among other things the new Act provided that:

> The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof. . . . Any order under this subsection shall state the findings upon which it is based. 21 U.S.C. § 355(e).

The Act defined the term "substantial evidence" as follows:

> As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. 21 U.S.C. § 355(d).

The proceedings to withdraw approval of the petitioner's CVP drug applications were under 21 U.S.C. § 355(e).

By notice in the Federal Register on July 9, 1966 the Commissioner announced that the National Academy of Sciences—National Research Council (NAS-NRC) had "agreed to assist the Food and Drug Administration in its review of the claims of effectiveness for drugs cleared through the new-drug procedures from 1938 until October 10, 1962." 31 Fed. Reg. 9426. The notice directed holders of such approved new-drug applications to submit certain specified data and material to NAS-NRC, in order to

> facilitate this review and a determination of whether there may be ground for invoking section 505(e) of the Federal Food, Drug, and Cosmetic Act, and to provide each holder of such an approved new-drug application an opportunity to present for the consideration of the reviewing experts the best data available to support the medical claims. . . .

Among the materials to be submitted were:

> f. Current labels and package inserts (attach 10 copies of each to original of form; 1 copy of each to duplicate).
>
> g. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, package insert, or brochure. Approximately 5 to 10 key references, if available (attach 10 copies of the list to original of form and 1 copy to duplicate).
>
> h. Unpublished articles or other data pertinent to an evaluation of the claims (one copy only; attach to duplicate).

Responding to the Commissioner's notice of July 9, 1966 USV submitted two bibliographies, one containing nine references, the other sixteen. This submission was reviewed by two NAS-NRC panels which in due course reported to

the Commissioner. The complete report of the Panel on Drugs Used in Hematologic Disorders was as follows:

C.V.P. with VITAMIN K
NDA 9965
LOG 734

Panel on Drugs Used in Hematologic Disorders

INDICATIONS

I. As a supplementary source of bioflavonoids, ascorbic acid, and menadione.
EVALUATION: Ineffective.
COMMENTS: The label correctly states that the dietary need for these agents has not been established, in agreement with Burns.

DOCUMENTATION:

1. Burns, J. J. Water-soluble vitamins; II. ascorbic acid (vitamin C), pp. 1673-1680. In L. S. Goodman and A. Gilman, Eds. The Pharmacological Basis of Therapeutics. (3rd ed.) New York: The MacMillan Co., 1965.

Approved by William [illegible]
Chairman

So far as material the report of the Panel on Drugs Used in Metabolic Disorders was as follows:

DUO-C.V.P.
NDA 9965
LOG 733

Panel on Drugs Used in Metabolic Disorders

INDICATIONS

None.

GENERAL COMMENTS

I. There is no package insert, but just a label indicating that this is a "supplementary source of bioflavonoids and ascorbic acid." There is no

definite claim for therapeutic use and a statement on the label admits that "the need for bioflavonoids in human nutrition has not been established." However, the inference is that there is indeed a need for such a product. The references support this inference, in that everything from threatened abortion to bleeding gums is reported to have responded. The use of these materials as hemostatic agents for capillary fragility is felt to be unjustifiable and not proved. The Panel recommends that there should be a clear statement as to the use of this preparation.

II. The Panel finds that the term "minimum daily adult" requirement is meaningless because variations in nutritional needs depend on the health, sex, age, and physical activity of the individual. The term "dietary allowances" is preferred.

III. See the general statement on multiple-vitamin preparations.

Approved by D. H. Nelson
Chairman

On January 23, 1968 the Commissioner announced that the Food and Drug Administration, having received the NAS-NRC report, "has considered the report and has concluded on the basis of the report and its own evaluations that there is no evidence that * * * bioflavonoids are effective for use in man for any condition." 33 Fed. Reg. 818. The Commissioner noted that lack of substantial evidence of effectiveness of a drug was a basis for withdrawing approval of a new-drug application, and that the Commissioner intended "to publish a notice of opportunity for a hearing on a proposal to withdraw approval" of new-drug applications for the bioflavonoids. The Commissioner stated, however, that before taking such action he invited all interested holders of new-drug applications to attend

a meeting on January 31, 1968 "to discuss the procedural matters involved in the proposed action * * * and to attempt to identify and resolve problems that may be anticipated as a result of the actions to be taken." The meeting was held on January 31, 1968 at which time the Food and Drug Administration again invited the submission of additional scientific and medical information that might be pertinent to the question of the effectiveness of the drugs. In response, USV submitted certain additional information in the form of reports and reprints.

By notice published in the Federal Register on July 10, 1968, 33 Fed. Reg. 9908, the Commissioner announced that "[t]he additional information received, considered together with other information available, did not provide substantial evidence of effectiveness of such drugs for use in man for any condition." Accordingly, the Commissioner gave notice that he proposed to withdraw approval on the ground that there was a lack of substantial evidence that any bioflavonoids had the effect which the drugs purported or were represented to have under the conditions for use prescribed, recommended or suggested in the labeling thereof, or that such articles alone, or as added components with other drugs, were effective for use in man in any condition. Continuing, the notice stated that "the Commissioner will give each applicant and any interested person who would be adversely affected by an order withdrawing such approval an opportunity for a hearing at which time such persons may produce evidence and arguments to show why approval of any new-drug application listed herein should not be withdrawn." 33 Fed. Reg. 9909.

On August 6, 1968 the petitioner filed an action in the United States District Court for the Eastern District of Virginia seeking a declaratory judgment that none of its products named in the Commissioner's notice was a new drug within the meaning of the Federal Food, Drug and Cosmetic Act, as amended. *USV Pharmaceutical Corp.* v.

Richardson, Civ. No. 4915-A (E.D. Va.).[3] On the following day, August 7, the petitioner requested the Commission to stay all further proceedings under the Commissioner's notice of July 10, 1968, pending the disposition of the declaratory judgment action. In addition to this request the petitioner on August 9, 1968 requested a hearing before the Commissioner on his proposal to withdraw approval of the petitioner's new-drug applications. On August 16 the Commissioner refused to stay the proceedings, stating:

> The National Academy of Sciences-National Research Council reported that there is no evidence that bioflavonoids are effective for use in man for any condition. This proceeding was initiated to provide an opportunity, to all interested parties, for a hearing on the proposal. This proceeding will afford you both an administrative hearing and an opportunity for judicial review if withdrawal of the new drug applications follow [*sic*].

The regulations in force in 1968 provided that upon timely request for a hearing "a hearing examiner will be named and he shall issue a written notice of the time and place at which the hearing shall commence. . . ." The date of the hearing was required to be not more than 120 days after the date of the Commissioner's notice of proposed withdrawal of approval "unless the hearing examiner and the applicant otherwise agree." 21 C.F.R. § 130.14 (1968). The Commissioner, however, did not name a hearing examiner and no further action was taken in the administrative proceedings until 1970.

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[3] After a hearing the District Court held, on April 1, 1971, that USV's bioflavonoid products were not "new drugs" within the statutory definition. On May 24, 1972 the Circuit Court of Appeals for the Fourth Circuit reversed, rejected the claim for exemption, and directed the district court to enter judgment for the defendants. *USV Pharmaceutical Corp.* v. *Richardson*, No. 71-1596 (4th Cir., May 24, 1972).

On May 8, 1970 the Commissioner revised the regulations governing hearings in NDA revocation proceedings. The revised regulations provide that a request for a hearing must state the reason why an NDA should not be withdrawn, "together with a well-organized and full-factual analysis of the clinical and other investigational data [the applicant] is prepared to prove" and setting forth "specific facts showing that there is a genuine and substantial issue of fact that requires a hearing." The regulations further provide that:

> When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data. 35 Fed. Reg. 7252 (1970); 21 C.F.R. § 130.14(b).

On July 7, 1970 the Commissioner wrote to the petitioner referring to the Commissioner's notice of proposed withdrawal published July 10, 1968 (33 Fed. Reg. 9908), the petitioner's request for a hearing dated August 9, 1968, and the revised regulations of May 8, 1970. The letter continued:

> The May 8 regulations are applicable to any request for a hearing. You should amend your request for a hearing to comply with those regulations, i.e., by submitting a well-organized and full-factual analysis of the clinical and other investigational data you are prepared to prove in a hearing, setting forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing.

Replying to the Commissioner's letter of July 7, the petitioner by letter dated August 7 requested a stay of all further proceedings before the Commissioner because (1) the petitioner's action for declaratory judgment in the Eastern District of Virginia, in which the petitioner asserted that its drugs were not "new drugs", was scheduled for trial on October 23, 1970, and (2) the validity of the revised regulations of May 8 was under challenge in the United States District Court for the District of Delaware.[4] In conclusion, USV requested "that if a stay is denied the company be given at least thirty days from receipt of notice of the denial to file a further response to your letters of July 7."

On October 14, 1970 the Commissioner replied to the petitioner's letter of August 7. The Commissioner noted that his letter of July 7 "suggested the request for a hearing be amended within 30 days from receipt of that letter" but that no amendment had been received.

> Accordingly, [said the Commissioner,] we conclude that no useful purpose will be served by further delaying the processing of a final order to withdraw approval of the subject new drug applications. The pending litigation in the United States District Court for the Eastern District of Virginia and the United States District Court for the District of Delaware do not provide sufficient ground to further delay these proceedings.
>
> Your request for a 30-day extension, in the event of our denial of a stay, is also denied.

---

[4] The Commissioner's regulations and standards were challenged by other litigants in the federal courts. *See Upjohn Co.* v. *Finch*, 422 F.2d 944 (6th Cir. 1970); *Pharmaceutical Manufacturers Ass'n* v. *Finch*, 307 F. Supp. 858 (D. Del. 1970); *Pharmaceutical Manufacturers Ass'n* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970). The challenges were unsuccessful.

On October 15, 1970 the Commissioner issued an order withdrawing the petitioner's NDAs. The ground of the order was stated to be that the Commissioner:

> finds that on the basis of new information before him with respect to each of said drugs, evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof. 35 Fed. Reg. 16332.

We think the procedures followed by the Commissioner were fundamentally defective.

The Commissioner acted pursuant to 21 C.F.R. § 130.14, the regulation establishing a summary judgment procedure for the Food and Drug Administration.[5] This regulation is modeled after Rule 56 of the Federal Rules of Civil Procedure, the summary judgment rule of the federal district courts. As counsel for the government stated at oral argument, the agency's procedure is analogous to the procedure under Rule 56. A vital distinction, however, is that the Commissioner here was not an impartial arbiter of the con-

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[5] 21 U.S.C. § 355(e) grants applicants the right to "due notice and opportunity for hearing" prior to withdrawal of approval to market new drugs in interstate commerce. We do not construe this section as precluding the use of summary judgment in appropriate circumstances, but it does restrict the application of that procedure to cases in which no material factual issue is presented and a hearing would be a hollow formality. *See Pennsylvania Gas and Water Co.* v. *Federal Power Comm'n*, No. 71-1126, 6-7 (D.C. Cir. decided May 2, 1972); *cf. Fidelity & Deposit Co.* v. *United States*, 187 U.S. 315, 320 (1902); 6 J. MOORE, FEDERAL PRACTICE § 56.06, at 2075-80 (2d ed. 1966).

See Gellhorn & Robinson, *Summary Judgment in Administrative Adjudication*, 84 Harv. L. Rev. 612 (1970), for a discussion of the use of summary procedures in administrative adjudications.

tentions of opposing parties, but was himself the moving party undertaking to support his own proposed order. The petitioner's applications had been approved, pursuant to 21 U.S.C.A. § 355(b) (1961), but now, under 21 U.S.C. § 355(e), the Commissioner proposed, without a hearing, to withdraw that approval on the basis of a new standard and new information, together with the evidence available when approval was originally granted. In this situation we think it was incumbent upon the Commissioner, before calling upon the petitioner for additional evidence establishing a right to a hearing, to state facts and reasons showing at least prima facie that the evidence before him raised no material issue of fact which would justify a hearing. This view of the Commissioner's burden is consistent with the practice under Rule 56 of the Federal Rules of Civil Procedure. Under that rule the moving party has the burden of presenting evidence that establishes his right to summary judgment as a matter of law; and he may not, by the bare assertion that he is entitled to summary judgment, shift to his opponent the burden of establishing the contrary. *Evers* v. *Buxbaum*, 102 U.S. App. D.C. 334, 253 F.2d 356 (1958); *Washington Post Co.* v. *Keogh*, 125 U.S. App. D.C. 32, 365 F.2d 965 (1966).

At no stage of this proceeding did the Commissioner present anything approaching a prima facie showing that there was no genuine and substantial issue of fact requiring a hearing. The reports of the NAS-NRC panels which we have quoted, and upon which the Commissioner relied in his notice of January 23, 1968, were cryptic and conclusory, without any statement of supporting facts. The Commissioner's notice of January 23, 1968 and his notice of July 10, 1968 parroted the language of the statute without reference to any evidence. In short, at no time did the Commissioner set forth the facts and reasons upon which he relied in reaching his conclusion that no material issue of fact existed. We think that such an application of the Commissioner's summary judgment rule is not in harmony with the

principle of the rule and is fundamentally unsound and unfair. Before calling upon the petitioner to answer, the Commissioner, as the moving party, had an obligation to present at least a prima facie case for denial of a hearing. *Cf. Greene* v. *McElroy*, 360 U.S. 474, 496 (1959); *Southern Railway Co.* v. *Virginia*, 290 U.S. 190, 197 (1933). Only after such a presentation could the Commissioner fairly impose upon the petitioner the heavy sanctions of 21 C.F.R. § 130.14.

By what we have said we do not intend to require a wholesale incorporation of the practice under the Federal Rules of Civil Procedure into administrative summary judgment proceedings; but the limited steps we have outlined are basic to administrative fairness.

The petitioner attacks the Commissioner's final order of withdrawal upon the further ground that it is not supported by adequate findings and conclusions. We agree. Both the statute, 21 U.S.C. § 355(e), and the Commissioner's own regulation, 21 C.F.R. § 130.14(b), require the Commissioner to state the findings upon which his order is based, and the summary judgment procedure did not excuse the Commissioner from that requirement. *Cf. NLRB* v. *Clement-Blythe Companies*, 415 F.2d 78, 81, 82 (4th Cir. 1969). Yet the Commissioner's order of October 15, 1970 merely tracks the language of the statute, stating in conclusory terms that there is a lack of substantial evidence that the petitioner's drugs are effective. As we have frequently emphasized, findings of fact are not mere procedural niceties; they are essential to the effective review of administrative decisions. Without findings of fact a reviewing court is unable to determine whether the decision reached by an administrative agency follows as a matter of law from the facts stated as its basis, and whether the facts so found have any substantial support in the evidence. *Saginaw Broadcasting Co.* v. *FCC*, 68 App. D.C. 282, 287, 96 F.2d 554, 559, *cert. denied*, 305 U.S. 613 (1938); *National Geographic Society* v. *District Unem-*

ployment Compensation Board, 141 U.S. App. D.C. 313, 438 F.2d 154 (1970); *Environmental Defense Fund, Inc.* v. *Hardin*, 138 U.S. App. D.C. 391, 397-98, 428 F.2d 1093, 1099-1100 (1970); *Greater Boston Television Corp.* v. *FCC*, 143 U.S. App. 383, 393, 444 F.2d 841, 851 (1970), *cert. denied*, 403 U.S. 923 (1971). Here we are left completely in the dark as to the facts and the evidence upon which the Commissioner based his judgment. Such a record cannot support the Commissioner's order.

Finally, the petitioner contends that the Commissioner acted arbitrarily by denying the petitioner's request for a stay and immediately thereafter entering a final order of withdrawal. Again, we agree. The request for a stay was not unreasonable and there is no suggestion that it was made in bad faith. In light of the leisurely if not dilatory pace at which the Commissioner had moved in the litigation —his failure to name a hearing examiner in response to the petitioner's demand of Augst 9, 1968, and his delay of more than two months in responding to the petitioner's August 7, 1970 request for a stay—the Commissioner's precipitous and summary action was arbitrary. In the circumstances we think petitioner was entitled to an opportunity to submit additional evidence or plead over when its request for a stay was denied. The Commissioner's explanation for his action, that further delay would serve no useful purpose, was a mere administrative ukase and amounted to no explanation at all.

We intimate no views as to the merits of this controversy over the effectiveness of the petitioner's drugs; the Commissioner's conclusions may well prove to be correct. We hold only that before entering his order he must conform to the requirements of administrative due process. This we think he has failed to do.

We set aside the Commissioner's order and remand the case for further proceedings in conformity with this opinion.

IT IS SO ORDERED.

APPENDIX I

Federal Food, Drug & Cosmetic Act (prior to October 10, 1962)
[Former Code Section Numbers Shown in Brackets]

Sec. 201[321]. For the purpose of this Act—

* * *

(p) The term "new drug" means—

(1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this chapter it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780:

* * *

Sec. 107. (a) Except as otherwise provided in this section, the amendments made by the foregoing sections of this part A shall take effect on the date of enactment of this Act.

(b) The amendments made by sections 101, 103, 105, and 106 of this part A shall, with respect to any drug, take effect on the first day of the seventh calendar month following the month in which the Act is enacted.

(c) (1) As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendments made by this Act to section 201 (p), and to subsections (b) and (d) of section 505, of the basic Act, insofar as such amendments relate to the effectiveness of drugs, shall not, so long as approval of such application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application, but shall apply to any changed use, or conditions of use, prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been

approved after the enactment date under section 505 of the basic Act as amended by this Act) until whichever of the following first occurs: (i) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

Federal Food, Drug & Cosmetic Act (21 U.S.C.), as Amended [Code Section Numbers Shown in Brackets]:

Sec. 201[321]. For the purposes of this Act—

* * *

(p) the term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling con-

tained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

OPPOSITION BRIEF

No. 75-[illegible]

In the

Supreme Court of the United States

October Term, 1975

ELLIOT RICHARDSON, Secretary of Health, Education and Welfare, and CHARLES C. EDWARD, Commissioner of Food and Drugs,

Petitioners,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED,

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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BRIEF FOR HYNSON, WESTCOTT AND DUNNING, INCORPORATED, IN OPPOSITION

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

ELLIOT RICHARDSON, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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BRIEF FOR HYNSON, WESTCOTT AND DUNNING, INCORPORATED, IN OPPOSITION

OPINIONS BELOW

The Opinion of the Court of Appeals (Pet., App. A, 1a) is reported at 461 F.2d 215. The Order of the Commissioner of Food and Drugs reviewed by the Court of Appeals was published in the Federal Register of June 18, 1971 (36 F.R. 11763, Pet., App. C, 14a-22a).

JURISDICTION

The judgment of the Court of Appeals was entered on May 24, 1972 (Pet., App. B, 12a). Mr. Justice Rehnquist extended the time to file a petition for certiorari to September 7, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1) and 21 U.S.C. 355(h).

STATUTES AND REGULATIONS INVOLVED

Section 505(e) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(e)) provides in part:

> "The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof * * *.

Section 505(d) (21 U.S.C. 355(d)) provides in pertinent part:

> * * * As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof.

Pertinent provisions of the regulations of the Commissioner of Food and Drugs, 21 C.F.R. 130.12(a)(5) and 130.14, as amended, 35 F.R. 7251, 7252, are set forth in Appendix A, infra, 1a.

QUESTIONS PRESENTED

Whether, despite the evidence submitted by Hynson, Westcott & Dunning, Incorporated, the Commissioner of Food and Drugs may, without a hearing, make a determination that there is a lack of substantial evidence of effectiveness of the drug Lutrexin, within the meaning of the Federal Food, Drug and Cosmetic Act (as amended by the Drug Admendments of 1962) and the Commissioner's regulations and, upon the basis of such determination, withdraw approval of the new drug application for such drug.

If the Government's petition should be granted we would want to place the following additional questions before this court which were argued in the court below:

1. Whether Hynson, Westcott & Dunning was entitled to a hearing by virtue of its timely acceptance of the proffered opportunity for a hearing under regulations then in effect, regardless of its rights under the regulations thereafter adopted under which a hearing was denied.
2. Whether the regulations under which a hearing was denied are valid.

STATEMENT

A. In the Statement in its petition the Government refers to "the mass of material" submitted by Hynson, Westcott & Dunning (HW&D) to the Food and Drug Administration (FDA) upon which the company relied as "substantial evidence" of effectiveness, declaring that

"Most of that material had previously been considered by the NAS-NRC panel" which found Lutrexin "possibly effective" (Pet. 9); and thereafter stating that the NAS-NRC panel had "little difficulty" concluding that the studies submitted "did not meet the medical community's standard of adequacy." (Pet. 14.)

In fact, only three of the fourteen studies (of which eleven were published), were considered by the NAS-NRC panel, *viz.*, two studies not identified by the panel by name and the study by S. S. Jones, *Lututrin, A New Drug for Relief of Dysmenorrhea.* (JA II, 92). None of the other studies (JA II, 1 et seq.) was considered.[1]

Of course, the affidavits of experts filed in HW&D's action in the District of Maryland (JA I, 38-94) were not before the NAS-NRC panel, having been executed long after the report of the panel was made to FDA.

The Government states that the Commissioner of FDA "demonstrated how each [study] showed deficiencies on its face that prevented it, under the rules, from being treated as an adequate and well-controlled study" (Pet. 9). This demonstration was not, however, convincing to the Fourth Circuit which thought that "whether the studies were as controlled as they might have been and whether there was a failure in these studies as published to fill in all the details the Commissioner might think appropriate are matters that could be developed at a hearing, after the authors were examined and the reliability of the investigations further inquired into" (461 F.2d 215 at 221-222; Pet. 1a, at 11a).

B. HW&D, in its Cross-petition for certiorari, filed on September 11, 1972, (No. 72-414) has presented questions of concern to many manufacturers and shippers of drugs, and to physicians who prescribe them, as con-

[1] Two of the studies were completed after the panel reported.

trasted with the matter before the court in the instant case, which involves essentially the question of whether the Commissioner acted arbitrarily in denying a hearing to HW&D on the particular facts before him.

ARGUMENT

Introduction

The Government's statement of the Question Presented is unacceptable in two respects. First, it assumes a failure to comply with the Commissioner's regulations and asks whether in such a case approval of a new drug application could be withdrawn without a hearing, thereby completely ignoring the matter of whether, in fact, there was such a failure to comply. Secondly, the Question is phrased as if there were involved a general principle of law of broad application whereas the real question is whether, *on the particular facts of this case*, the Commissioner could properly determine without a hearing that there was a failure to comply with the regulations.

This is not a case where the evidence, on its face, does not meet the applicable standards and therefore there are no facts to ascertain.[2] We shall show that the studies submitted by HW&D were of sufficient stature to require a hearing to determine whether they meet the standard of the FDA regulation, and that the Court's conclusion was correct that they raised a genuine and substantial issue of material fact as to the effectiveness of Lutrexin, within the meaning of the regulations.

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[2] As in *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192 (1956), where petitioner concededly "owned" more television stations than a rule of the Federal Communications Commission permitted; and *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33 (1964), where a petition was patently not in proper form because of certain price-changing provisions in the contracts filed with the petition, which were not permissible under a rule of the Commission.

I

THE COURT OF APPEALS WAS PLAINLY RIGHT IN HOLDING THAT HW&D HAD SUBMITTED TO FDA EVIDENCE RAISING A GENUINE AND SUBSTANTIAL ISSUE OF MATERIAL FACT ENTITLING HW&D TO A HEARING PRIOR TO WITHDRAWAL OF APPROVAL OF THE NDA FOR LUTREXIN.

FDA's regulations provide that in order for an NDA applicant to be entitled to a hearing on a proposal by the Commissioner of Food and Drugs to withdraw approval of an NDA, the applicant must come forward with "specific facts showing there is a genuine and substantial issue of fact that requires a hearing;" and the absence of adequate and well-controlled investigations to support claims of effectiveness is cited by FDA as an example of a defect in a request for a hearing which would result in denial of the request (21 CFR 130.14(b), App. A, infra, 4a). The regulations spell out in detail the principles FDA considers "essentials of adequate and well-controlled clinical investigations" (21 CFR 130.12 (a) (5), App. A, infra, 1a).

In the instant case, the Commissioner concluded that HW&D's response to the notice of hearing (JA I, 27) did not show that there was a genuine and substantial issue of fact which justified the holding of a hearing (Pet. App. C, 14a). The court below held that FDA erred in denying HW&D a hearing because the data submitted by the company did show the existence of a genuine and substantial issue of fact. For the reasons stated below we submit the court was plainly correct.

A. The Affidavits And Reports Of Medical Investigations Are Adequate Justification For A Hearing.

HW&D submitted with its response to the notice of hearing affidavits of six physician-experts in the field of

obstetrics and gynecology (OB/GYN)[3]. As noted by the court below, the government ". . . did not impugn the competency or qualifications" of these experts. "Their professional qualifications, as they appear in the record are impressive."[4] The six OB/GYN physicians have had extensive experience with Lutrexin in the treatment of dysmenorrhea and premature labor[5]. The affidavits show that the doctors have used Lutrexin in the treatment of a total of approximately three thousand patients with these disorders over the past fifteen years. The affidavits state without equivocation that Lutrexin is safe and effective for its intended uses.

The affiants' conclusions were not based merely on their clinical experience with Lutrexin, but also upon studies reported in the medical literature.[6] Eleven reports on Lutrexin have been published in authoritative professional medical journals and were submitted to FDA in support of HW&D's "request" for a hearing. Two unpublished investigations by OB/GYN experts were also placed before the agency. These studies provide a sound basis for the conclusions of HW&D's affiants that Lutrexin is both safe and effective for use in the treatment of dysmenorrhea and premature labor. For example, Dr. Gratton's paper[7] on Lutrexin reports on a study of 219 patients with a medical history of prior pregnancies tragically interrupted by miscarriage or premature labor.

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[3] JA I, 38-94.

[4] 461 F.2d 215, 221, Pet., App. B at 27a.

[5] Premature labor and dysmenorrhea are generally thought to result, at least in part, from abnormal or untimely contractions of the musculature of the uterus. The purpose of Lutrexin therapy is to quiet the uterus to prevent, in premature labor, a too-early birth, and, in dysmenorrhea, to relieve cramping and associated symptoms.

[6] These studies are reproduced in JA II.

[7] JA II, 1.

Less than 50% viable babies resulted from the prior untreated pregnancies of these patients. With use of Lutrexin, almost 80% viable babies were obtained. Dr. Rezek's paper[8] presents 54 cases of premature labor treated with Lutrexin. Premature labor was stopped in 74% of the patients for at least 28 days, thus ". . . enabl . . . [ing] many fetuses to survive that otherwise would have died because of prematurity" (JA II, 41). Other studies reported in the medical literature and submitted to FDA, demonstrate the safety and effectiveness of Lutrexin for use in treatment of dysmenorrhea,[9] and attest to the biological availability of the drug.[10]

B. FDA's Findings Concerning HW&D's Affidavits And Medical Studies Demonstrate The Existence Of Genuine And Substantial Issues Of Fact Requiring A Hearing.

In his order (Pet., App. C, 14a et seq.) withdrawing approval of the NDA for Lutrexin, the Commissioner denied HW&D a hearing on its contentions that the drug was not a new drug and that substantial evidence of effectiveness existed for the product, basing the denial primarily on the ground that no adequate and well-controlled clinical investigations had been proffered by HW&D. The Commissioner attempted to support the determination by a critique of the data submitted by HW&D, purporting to single out deficiencies in the design and performance of the investigations. The Court below made no distinction between the Commission's analysis of the studies in connection with HW&D's "new drug" contention (Pet. App. C, 16a-20a) and the analysis of the studies in connection with the "substantial evidence" contention (id. 20a-21a). For the purposes of

[8] JA II, 40.

[9] JA II, 33, 85, 92.

[10] JA II, 34 at 38, and 85 at 87 and 90.

this discussion, no distinction will be made between the two points involved." [11]

The Commissioner's analysis of HW&D's medical investigations raises substantial and complex issues of fact which cannot, as we shall show, appropriately be resolved by a reviewing court without the benefit of a record based upon expert evidence adduced at a hearing before FDA. This is not a case like *Pfizer, Inc.* v. *Richardson*, 434 F.2d 536 (2d Cir. 1970) where the court could say ". . . it is apparent even to us laymen that the FDA had a reasonable basis for considering that Pfizer's submissions did not comply with the requirement of the statute and the Regulation" (434 F.2d at 546-547). Nor is it a case like *Upjohn Company* v. *Finch*, 422 F.2d 944 (6th Cir. 1970) where the company, according to FDA's final order, recognized that its studies did not meet the adequate and well-controlled criteria in FDA's regulations but argued that the studies plus clinical experience with its drugs amounted to substantial evidence (422 F.2d at 958).[12] The instant case, by contrast, involves medical

[11] There is, however, a fundamental distinction of importance, shown in HW&D's Cross-Petition herein, (No. 72-414), between the evidence required for proof of general recognition of safety and effectiveness, the test for a "new drug", and proof of actual effectiveness by adequate and well-controlled studies, the substantial evidence test. As was pointed out in our briefs in the court below, there is no basis in the statute or legal precedent, for the proposition that substantial evidence of effectiveness must be shown to prove a product not to be a new drug. The courts have specifically rejected the proposition. *United States* v. *Articles of Drug Labeled "Quick O-ver"*, 274 F. Supp. 443, 445-446 (D. MD. 1967); *Amp Incorporated* v. *Gardner*, 389 F.2d 825, 831 (2d Cir. 1968), cert. denied sub nom *Amp. Inc.* v. *Cohen*, 393 U.S. 825, rehearing denied 395 U.S. 917; *United States* v. *An Article of Drug*** Excedrin P.M.*, CCH Food, Drug & Cosmetic Law Reporter 40, 486 at page 41, 226 (D. N.Y. 1971, No. 70-C-77); *United States* v. *Article of Drug, Etc.*, 294 F. Supp. 1307, 1310 (D. Ga. 1968).

[12] In *Upjohn* the agency permitted the company to make an oral presentation on the factual issues involved.

evidence which, as we shall show, cannot on its face be reasonably judged as failing to meet the requirement of "substantial evidence". Encompassed within this issue is the factual and legal question, raised in HW&D's affidavits, of whether medical ethics proscribe investigations other than the type submitted by HW&D.

(1) *Historical Controls*

FDA's regulations defining "adequate and well-controlled studies" require that a medical investigation contain a method of selection of the subjects that ". . . provides a comparison of the results of treatment . . . [using the drug under investigation] with a control in such a fashion as to permit quantitative evaluation" (21 C.F.R. 130.12(a)(5)(ii)(a)(4), App. A, infra, 1a-2a). One method of control acceptable to the agency is historical control:

> "Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen . . . the effectiveness of which is established" (21 C.F.R. 130-.12(a)(5)(ii)(a)(4)(iv), App. A, infra, 3a).

It cannot be gainsaid that premature labor and threatened and habitual abortion are conditions involving a "high and predictable mortality" as well as conditions "where morbidity is predictable." If premature contractions of a gravid uterus are not halted, a dead fetus is certain.

The necessity of performing certain tests using historical controls is described by Dr. Allen who was a member of the NAS/NRC panel which reviewed Lutrexin:[13]

> "There is a good deal of uncertainty regarding what type of study should be carried out in order to fully establish the validity of the results. In these studies the patient herself serves as the control; the results in the pregnancies prior to the treated pregnancy are compared with the results in the treated pregnancy. A supposedly better method of study which is popular today would utilize the placebo method; one patient receives the hormone and the next patient the placebo, the investigator not knowing which patient received the placebo until the study is complete. This type of study is now so 'sacred' that any other type is often not recognized as investigative. However, there are many clincial problems in which this type of study violates the rules of clinical morality as well as common sense. Let us consider some disease in which the risk of death is appreciable, lobar pneumonia, for example. No clinician could risk treating alternate cases with an antibiotic and a placebo. In such a study the risk of death while receiving the placebo might be as much as 25 per cent. In the study of habitual abortion the risk of death to the fetus in

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[13] Dr. Allen also is on record in support of the continued marketing of Lutrexin. He has stated, in a notarized letter to HW&D:

> "Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of laboratory animals and women". * * * "The clinical evidence which you have submitted [to me] . . . does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates that Lutrexin is not harmful or dangerous either to the patient or to the fetus. You have submitted no evidence that Lutrexin is ineffective, nor do I know of any evidence in the medical literature indicating that it is ineffective." * * * "Lutrexin, since it contains an active principal which relaxes the uterus, should be available for the treatment of premature labor . . ." JA I, 60-61.

utero is between 80 to 90 per cent. It seems to me that one no longer has the right to use a placebo as a control because the data already available from the studies in which the patient serves as her own control indicate that the fetal losses are reduced from 80 or 90 per cent to 25 per cent or perhaps less."[14]

HW&D's Investigations

In Dr. Gratton's study,[15] which involved habitual aborters, the patients were used as their own controls, and the results of Lutrexin treatment vis a vis prior untreated pregnancies were statistically evaluated:

". . . in the 219 patients with a total of 446 pregnancies, there were only 46% live births prior to the use of Lutrexin. Following the administration of Lutrexin, the percentage of live births in these same patients was 79.8% with a probability of .001. Probabilities ranging from .001 to .05 were observed in women with one to five pregnancies who had been treated with Lutrexin" (JA II, 2-3).

In Dr. Majewski's first two studies,[16] which involved premature labor, the results were compared with the documented history of premature births in the hospital where the study was performed:

"The hospital wherein the study was conducted has . . . a premature birth rate of 9.7 per cent by length of gestation and 6.2 per cent by weight. During a four-month period in 1953, the premature birth rate by history was 9.7 per cent in 1601 deliveries. During the same period, there were 101 premature births by weight, or 6.3 per cent. During this study there were, in a comparable period during 1954, 154 births premature by history in a total of 1631 deliveries,

[14] JA II, 52-53. This paper is not a report on Lutrexin.

[15] JA II, 1.

[16] JA II, 7, 15.

> for a percentage of 9.4. In our series of patients using the uterine relaxing factor [Lutrexin] the number of premature deliveries by weight was reduced during these four months to 80 (4.9 per cent), a saving of 21 premature deliveries" (JA II, 9).

In Dr. Majewski's second study,[17] which is a continuation of the first study, the comparison was enlarged to one of the total number of premature survivals, stillbirths and neonatal deaths during the 15-month period the study was in progress. In Dr. Majewski's third study the results were compared statistically with the results of prior untreated pregnancies (JA II, 29).

The studies by Drs. Rezek, Gray, Trythall, G. Jones et al., and S. Jones do not purport to be controlled studies,[18] but they are "clinical investigations" within the meaning of the definition of "substantial evidence" in Section 505(d) and should be so recognized by FDA. Instead, the FDA regulations merely state that such investigations "may provide corroborative support of well-controlled studies regarding efficancy and may yield valuable data regarding efficacy of the test drug" (21 C.F.R. 130.12(a)(5)(ii)(c), App. A, infra, 1a).

FDA's Findings

We have referred to the fact that, in its withdrawal order, FDA offered a critique of the HW&D studies to support its conclusion that they were not adequate and well-controlled investigations and, therefore, that no hearing was required. A review of some of the specifics of the critique clearly reveals, however, that genuine and substantial issues of fact do exist between FDA and HW&D. FDA said, for example:

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[17] JA II, 15.

[18] The G. Jones et al study (JA II, 85) does, however, contain a small controlled study of the biological availability of Lutrexin.

(1) With respect to Dr. Majewski's first two studies:[19] "* * * Six patients received the drug for less than three hours, which the authors without explanation considered too short a time for a true test of effectiveness". (Pet. App. C, at 17a);

(2) With respect to Dr. Majewski's third study:[20] "Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided. * * * The data in Table I does not admit of statistical evaluation by the chi square test since the test is based on the assumption that each number in the columns of Table I is the sum of independent yes or no responses . . ." (Pet., App. C, at 18a).

(3) With respect to Dr. Rezek's first study:[21] Concomitant medication is not excluded * * * No explanations of the methods of observation, the recording of results, and steps taken to minimize patient and investigator bias are provided" * * * (Pet., App. C at 19a).

(4) With respect to Dr. Gratton's study:[22] The pairings of live births percentages in Table II cannot be compared since the number of previous pregnancies differs between the pair percentages and there is no data on possible etiologic factors of previous abortions and premature labor" (Pet., App. C at 19a).

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[19] JA II, 7, 15.

[20] JA II, 23.

[21] JA II, 34.

[22] JA II, 1.

These purport to be findings of facts which obviously are considered material by FDA.

These unsupported findings raise issues of fact which can only be resolved by expert testimony at a hearing before FDA. As stated by the Court below:

> "Assuming that all the objections by the Commissioner . . . may have some validity, they do not justify a final conclusion . . . that it 'clearly appears' that there is no genuine issue of fact . . .; at most, they merely create a genuine question of fact to be resolved at a hearing upon proper evidence" (Pet., App. A, 11a).

Without the benefit of a full record based upon expert testimony as to the medical and scientific validity of FDA's objections and the affidavits and studies themselves, a reviewing court is not in a position to decide the complex questions involved. Criticisms such as "the data . . . does not admit of statistical evaluation by the chi-square test . . ." raise questions of fact which can be resolved only by experts. Under the circumstances of this case, FDA's order cannot be given the usual deference accorded orders of "expert" administrative agencies; nor are its findings of fact to be considered conclusive under Section 505(h), because the order is not based upon substantial evidence of record adduced at an adjudicative hearing before the agency.

II

THE NATURE OF THE FDA "SUMMARY DECISION" PROCEDURES EMPHASIZES THE NECESSITY FOR A HEARING ON THE EFFECTIVENESS OF LUTREXIN.

HW&D argued in the Court below that FDA, under its procedures (App. A, 4a) is both litigant and judge; that FDA argues, as a litigant, that no genuine issue

of fact exists and then, proceeds, as judge, to uphold its own argument; and that such a combination of advocating and judging violates fundamental principles of fairness and due process.

Given this kind of procedure it is submitted that, at the very least a hearing is required at which the experts can be examined to determine whether their studies constitute substantial evidence of the effectiveness of Lotrexin and at which they can explain the basis for the opinions set forth in their affidavits. As the Court of Appeals for the District of Columbia circuit recently said, with reference to the same FDA procedure:

> "As counsel for the government stated at oral argument, the agency's procedure is analagous [sic] to the procedure under Rule 56. A vital distinction, however, is that the Commissioner here was not an impartial arbiter of the contentions of opposing parties, but was himself the moving party undertaking to support his own proposed order." [23]

We are aware that some agencies, including the Federal Trade Commission and the National Labor Relations Board, provide for administrative summary decision or judgment in their regulations; [24] and that the Administrative Conference of the United States recommended a rule for summary decision in agency adjudication at its Fourth Plenary Session, June 2-3, 1970, in Washington, D.C.[25] These agency regulations and the Administrative Conference recommendation, however, contemplate that

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[23] *USV Pharmaceutical Corporation* v. *Secretary of Health, Education and Welfare*, No. 24, 900, D.C. Cir., decided August 14, 1972 (Slip op., p. 11).

[24] FTC: 16 C.F.R. 3.24; NLRB: 29 C.F.R. 102.24-28, in particular section 102.24.

[25] The recommendation (No. 20) is set forth in Gellhorn and Robinson, *Summary Judgment in Administrative Adjudication*, 84 Harvard Law Review 612, 628-629 (1971).

the party desiring summary decision make a motion for such a decision before a hearing examiner or presiding officer appointed to conduct the hearing and that the essential facts upon which the motion is based be placed before the examiner, who may call for argument and the submission of briefs.

The FDA regulations, although purportedly based upon Civil Rule 56, make no provision for such procedure. No examiner is appointed to hear an FDA motion and no affidavits or other evidence are presented by FDA to show the absence of a genuine and substantial issue of material fact. FDA simply decides that there is no such issue.

Moreover, no discovery procedures are provided by FDA to the party opposing summary decision. Yet, concededly, the summary decision rule is inapplicable to proceedings lacking or restricting discovery procedures.[26]

It is clear that a basic motivation, if not the principal one, for the FDA order withdrawing approval of the NDA for Lutrexin was the opinion of the NAS-NRC panel that Lutrexin was "possibly effective" and that the claims for the drug were not adequately supported. In fact, the report of the panel was the only "evidence" before FDA other than that provided by HW&D.

As we have noted, only three of the reports of the fourteen studies set forth in Volume I of the Joint Appendix were before the panel. It was therefore important to HW&D to inquire into the decision-making process which led to the withdrawal order. In response to inquiry by HW&D, dated August 18, 1969, the Acting

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[26] Gellhorn & Robinson, *Summary Judgment in Adjudication*, supra, at 618. The authors note (p. 618, footnote 29): "In the federal courts summary judgment has long been denied where the party opposing the motion is barred from access to rebuttal information . . ."

Associate Director of Information for Public Services of the Department of Health, Education and Welfare replied, by letter of September 18, 1969 (see Appendix B, infra, 6a et seq.), that neither FDA nor the Department has "any report of any deliberations, minutes, notes, or other material of the National Academy of Sciences—National Research Council Panel . . ."; that neither FDA nor the Department "has any statement, other than the reports themselves, reflecting the view of each member of the panel concerning the effectiveness of Lutrexin . . ."; [27] that "other than the references listed under the heading, Documentation, by the Panel in its reports on Lutrexin . . . we do not know what medical or scientific literature was relied upon by the Panel"; and that FDA "has not conducted any independent clinical study or other scientific investigation of Lutrexin . . . at any time."

Thus, one of the principal supports of the FDA withdrawal order was formulated without the benefit of most of the available literature on Lutrexin and we do not know how or by what vote the panel reached its decision. Had the NAS-NRC panel had the benefit of such literature reflecting the conclusions that the clinical experts have reached, its evaluation would, we believe, have been that the drug is effective as claimed. The final evaluation of FDA might therefore have been entirely different. All that HW&D asks this Court, therefore, in this brief, is that the government's petition be denied so that the experts can be examined at a hearing to determine the validity and significance of their studies and of the opinions expressed in their affidavits.

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[27] This point was important because, of the five members of the panel, only two were specialists in Obstetrics and Gynecology.

III

THE ESTABLISHED CRITERIA FOR REVIEW BY THIS COURT ARE NOT MET IN THIS CASE.

The Government states that the evidence on which the court here relied "is a type of evidence that very likely can be produced by the manufacturer in virtually every withdrawal proceeding" (Pet. 16). The facts do not support that statement. Thus, in similar situations no evidence comparable to that submitted by HW&D was submitted to FDA by Ciba-Geigy Corporation (see *Ciba-Geigy Corp.* v. *Richardson*, 446 F.2d 466, 467 (2d Cir. 1971)), or by American Cyanamid Company (see *American Cyanamid Company* v. *Richardson*, 456 F.2d 509, 511-12 (1st Cir. 1971).

The cases just cited, together with *Upjohn Company* v. *Finch*, 422 F.2d 944 (6th Cir. 1970) and *Pfizer, Inc.* v. *Richardson*, 434 F.2d 536 (2d Cir. 1970), cited by the government, emphasize the point made at the outset of this Argument: that there is involved here, not a general principal of law of broad application, but the question whether, on the particular facts of this case, the Commissioner could properly determine without a hearing that there was a failure to comply with FDA regulations.

In *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192 (1956) and *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33 (1964), it was held that an agency may refuse a hearing upon applications which fail to conform to criteria established by regulations pursuant to the pertinent statute; but in those cases it was neither conceded nor obvious that the applications failed to conform.

The Government also cites *Ciba-Geigy Corp.* v. *Richardson*, supra, where failure to conform to the rule was obvious. There the court said:

> "In the present case Ciba could have obtained a hearing simply by compiling and presenting the evidence needed to make out a prima facie case. No valid reason is offered for its not doing so. Thus it was afforded the opportunity for a hearing to which it was entitled under Section 505(e) of the Act, 21 U.S.C. Section 355(3)" (466 F.2d at 468).

The courts in *Upjohn* and *Pfizer* were satisfied that the evidence before the Commission brought those cases within the principal enunciated in *Storer*, *Texaco* and *Ciba* and there was reason for this view, as discussed in Point I, supra. The facts before the Commissioner in each of the FDA cases discussed (*Ciba-Geigy*, *American Cyanamid*, *Upjohn* and *Pfizer*) were different and the facts in the instant case are different from those in the other cases cited.

In the instant case, we believe that the Court of Appeals for the Fourth Circuit was correct in its conclusion that the evidence presented a genuine and substantial issue of material fact, for the reasons stated in Point I.

We conclude, therefore, that the decision does not, as the Government states (Pet. 19) conflict with *Pfizer, Inc.* v. *Richardson* or *Upjohn Co.* v. *Finch*, supra, or with *Pharmaceutical Manufacturers Ass'n.* v. *Richardson*, 318 F. Supp. 301 (D. Del., 1970).[28]

The Government expresses apprehension that, if the basis of the reasoning and decision of the court below is adopted, FDA would be swamped with hearings. Even

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[28] This was an action for declaratory and injunctive relief in which the FDA regulations were upheld. The court there specifically distinguished the "abstract setting as presented here" from a "definitive factual situation" where the reviewing Court could determine whether the Commissioner correctly applied his regulations (318 F. Supp. 301 at 313).

if true, this is not of itself a valid reason for denying HW&D a hearing. As the Court of Appeals for the Third Circuit said in *Mississippi River Fuel Corp.* v. *Federal Power Commission*, 202 F.2d 899 (3d Cir. 1953):

> "We can understand, as the argument in this case has seemed to imply, that the Commission may have had to contemplate serious injury to the public interest because of its inability with very limited funds and staff to perform the enormous task of investigation and analysis imposed upon it in times when so many public utilities are submitting important proposals within its jurisdiction and the statutory scheme requires it to act promptly or let proposals go by default. But the remedy lies with Congress. If changes in the law are needed, or more personnel to administer existing law, or both, it is not for the administrative agency or the courts to try to make up for this deficiency by taking unauthorized short cuts or indulging time saving procedures which fail to accord parties the rights which the law as written gives them." (202 F.2d at 902-903).

In any event, the question whether, on complex medical facts which vary from case to case, the Commissioner is justified in concluding that no genuine and substantial issue of material fact was present, does not seem to be the kind of matter which qualifies for review by this Court. On this point the Court has said:

> ". . . it is very important that we be consistent in not granting the writ of certiorari except in cases involving principles the settlement of which is of importance to the public, as distinguished from that of the parties, and in cases where there is a real and embarrassing conflict of opinion and authority between the Circuit Courts of Appeals." [20]

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[20] *Layne & Bowler Corporation* v. *Western Well Works*, 261 U.S. 387, 393 (1923).

CONCLUSION

For the foregoing reasons it is submitted that the petition for certiorari should be denied.

Respectfully submitted,

EDWARD BROWN WILLIAMS

Counsel for Hynson, Westcott & Dunning, Incorporated

APPENDIX A

21 C.F.R. 130.12(a)(5), as amended, 35 F.R. 7251, provides:

§ 130.12 Refusal to approve the application.

(a) * * *

(5) (i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.

(*a*) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(*1*) A clear statement of the objectives of the study.

(*2*) A method of selection of the subjects that—

(*i*) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic

criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired.

(*ii*) Assigns the subjects to test groups in such a way as to minimize bias.

(*iii*) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.

(*3*) Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjective response, and steps taken to minimize bias on the part of the subject and observer.

(*4*) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparison are recognized:

(*i*) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

(*ii*) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(*iii*) Active treatment control: An effective regimen of therapy may be used for comparison, e.g.,

where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(*iv*) Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

(*5*) A summary of the methods of analysis and an evaluation of data derived from the study, including any appropriate statistical methods.

Provided, however, That any of the above criteria may be waived in whole or in part, either prior to the investigation or in the evaluation of a completed study, by the Director of the Bureau of Drugs with respect to a specific clinical investigation; a petition for such a waiver may be filed by any person who would be adversely affected by the application of the criteria to a particular clinical investigation; the petition should show that some or all of the criteria are not reasonably applicable to the investigation and that alternative procedures can be, or have been, followed, the results of which will or have yielded data that can and should be accepted as substantial evidence of the drug's effectiveness. A petition for a waiver shall set forth clearly and concisely the specific provision or provisions in the criteria from

which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been, employed, what results have been obtained, and the basis on which it can be, or has been, concluded that the clinical investigation will or has yielded substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(*b*) For such an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(*c*) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

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21 C.F.R. 130.14(b), as amended, 35 F.R. 7252, provides:

§ 130.14 Contents of notice of hearing.

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(b) If the applicant elects to avail himself of the opportunity for a hearing, he is required to file a

written appearance requesting the hearing within 30 days after the publication of the notice and giving the reason why the application should not be refused or should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the notice of opportunity for a hearing. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data. If a hearing is requested and is justified by the applicant's response to the notice of hearing, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree.

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APPENDIX B

[SEAL]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Sep. 18, 1969

J. H. Fitzgerald Dunning, President
Hynson, Westcott & Dunning, Inc.
Pharmaceutical Laboratory
Baltimore, Maryland 21201

Dear Mr. Dunning:

This is in further response to your letter of August 18, 1969, requesting information pertaining to the report of the Panel on Drugs Used in Disturbances of the Reproductive System, National Academy of Sciences-National Research Council, on the products Lutrexin Tablets and Trexinest Tablets. Our reply to your specific requests is as follows:

1. Neither the United States Food and Drug Administration, the Consumer Protection and Environmental Health Service, nor the Department of Health, Education, and Welfare has a Curriculum Vitae of the chairman and members of the Panel.

2. A copy of the Panel report on Trexinest Tablets is enclosed.

3. Copies of the contract between the Food and Drug Administration of the National Academy of Sciences-National Research Council, Contract No. FDA 66-197 (NEG), dated April 29, 1966, and Supplemental Agreement No. 1, dated June 17, 1966, are enclosed.

4. No instructions were issued by the Food and Drug Administration or the Department of Health, Education, and Welfare other than the contract itself.

5. The Department of Health, Education, and Welfare and the Food and Drug Administration issued no instructions or guidelines to the Panel on Drugs Used in Disturbances of the Reproductive System, nor did they communicate in any way with the Panel respecting any efficacy study of any product, including Lutrexin Tablets and Trexinest Tablets. As far as this Department is aware, the only instructions to the Panel are found in the document, Guidelines for the Drug Efficacy Study of the National Academy of Sciences-National Research Council; a copy of those "Guidelines" is enclosed.

6. The Food and Drug Administration, the Consumer Protection and Environmental Health Service, and the Department of Health, Education, and Welfare do not have any report of any deliberations, minutes, notes, or other material of the National Academy of Sciences-National Research Council Panel. The National Academy of Sciences-National Research Council Drug Efficacy Study Group may be able to inform you whether or not such documents exist.

7. Other than the references listed under the heading, Documentation, by the Panel in its reports on Lutrexin and Trexinest, we do not know what medical or scientific literature was relied upon by the Panel.

8. Neither the Food and Drug Administration, the Consumer Protection and Environmental Health Service, nor the Department of Health, Education, and Welfare has any statement, other than the reports themselves, reflecting the view of each member of the Panel concerning the effectiveness of Lutrexin and Trexinest.

9.-11. We have no information concerning whether the Panel solicited opinions from outside consultants, the manner in which the Panel's conclusion was reached, or whether any independent clinical studies of the effectiveness of Lutrexin and Trexinest were made by the Panel or on its behalf.

12. The Food and Drug Administration has not conducted any independent clinical study or other scientific investigation of the effectiveness of Lutrexin and Trexinest at any time.

13. (a) and (b) The information submitted by your firm to the Food and Drug Administration by letters dated July 22, 1968, and November 1968 was not submitted to the Panel, since the Panel had concluded its report and had it submitted to the Food and Drug Administration prior to May 23, 1968, the date the report was sent to your firm.

(c) Your firm has elected to avail itself of the opportunity for a hearing on the question of withdrawal of approval of the New Drug Applications for Lutrexin and Trexinest. As you know, there is no provision for prehearing discovery in the rules of practice which govern such hearings. Written reports and memoranda prepared by Food and Drug Administration personnel prior to the issuance of the Federal Register announced affording your firm an opportunity for a hearing on the withdrawal of the approval of the New Drug Applications for these drugs are internal-working papers which are specifically exempt from disclosure by the Public Information Act, 5 U.S.C. 552(b)(5). The official responsible for the final decision of any Food and Drug Administration action is Dr. Herbert L. Ley, Jr., Commissioner of Food and Drugs.

Sincerely yours,

/s/ Morton A. Lebow
MORTON A. LEBOW
Acting Associate Director of
Information for Public
Services